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Alkylation-Terminated Catellani Reactions Using Alkyl Carbagermatranes

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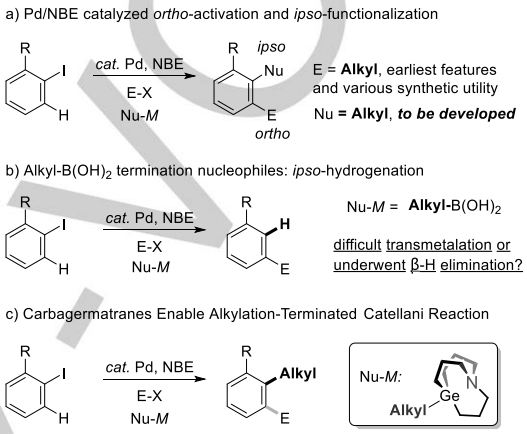
Abstract: Catellani reaction has received extensive attentions as it allows rapid multiple derivatization on aromatics. While using alkyl electrophiles to achieve *ortho*-alkylation is one of the earliest features of Catellani reaction, *beta*-H incorporated *ipso*-alkylation terminated reaction has not been realized to date. Herein, we report alkylation terminated Catellani reaction using alkyl carbagermatranes (alkyl-***Ge***) as nucleophiles. Reactivity of alkyl-***Ge*** and alkyl-$B(OH)_2$ in this reaction was also discussed. This reaction realized efficient *beta*-H incorporated dialkylation, which is inaccessible by Catellani reaction before.

Pd-catalyzed/NBE-mediated *ortho*-activation and *ipso*-functionalization reaction, also known as Catellani reaction,[1,2] features one of the most effective tools of constructing multiply substituted aromatics. The most prominent advantage of this type of reaction is that orthogonal combination of different *ortho*-reactions and *ipso*-reactions (termination reactions) allows a large number of difunctionalization patterns[3] (Scheme 1a). In the past few decades, the scope of *ortho*-reactions has been extended intensively from alkylation[1,4] to various recently developed electrophiles (E-X).[5] Meanwhile, termination reactions have been constantly emphasized throughout the developing history of Catellani reaction. Taking representative termination reactions as examples, Heck-type reaction was firstly applied in 1997[1] and the most applied to date in the termination event of Catellani reaction. Lautens elegantly demonstrated that by combining with tandem cyclization process,[6] Heck-type termination was successfully utilized in multiple complex molecule synthesis, also in which phosphine ligand was introduced for the first time providing more variables for optimization. Subsequently, using aryl boronic acid as the terminating reagent brought general method to the introduction of aryl rings.[7] Next, introduction of alkynyl group at *ipso* position was also realized using terminal alkynes.[8] A special type of termination reaction would be *ipso*-hydrogenation obtaining *meta*-substituted aromatic rings.[9] In 2015, by combining directed C-H activation with Pd/NBE catalysis, Yu and Dong independently realized *meta* C-H functionalization using NBE derivatives as transient mediator.[10] In addition, heteroatom-introducing termination has also enriched the content of Catellani reaction.[11] In particular, introduction of boron as a special heteroatom granted the potential of further functionalizations that might be inaccessible by direct termination.[12] Nevertheless, direct alkylating[13] termination by general alkyl nucleophiles[14] (especially the ones with *beta*-H) has not been reported yet.



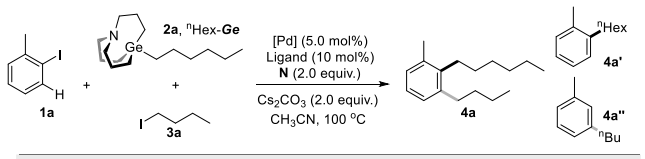
Scheme 1. Alkyl nucleophiles in Catellani reactions

While many challenges of Catellani reaction have been addressed, alkylation-terminated variants remain a challenge. We assume that the difficulties of alkylation terminated Catellani reaction probably stem from the requirement of transmetalation of alkyl group on the bulky 2,6-disubstituted Aryl-Pd(II) intermediate. For instance, Suzuki reaction, which has been remarkably successful regarding cross-coupling, however was less efficient (e.g. comparing to Heck type termination) in termination step of Catellani reaction. In fact, in the report by Catellani of *ortho*-alkylation/*ipso*-Suzuki-terminated difunctionalization, *ortho*-substituted aryl boronic acid was unsuccessful substrate,[7,15] suggesting that the efficiency of termination step is sensitive to the properties and structure of the nucleophiles. It is noted that, in 2005, Lautens' group discovered that the use of alkyl boronic acids in Catellani reaction would end up with *ipso* hydrogenated products (Scheme 1b).[9] It is noteworthy that modification of NBE[3b] has enabled significant challenges such as *ortho* mono-functionalization of haloarenes[16] to be overcome in the Catellani reaction. However, we assumed that such strategy may not significantly benefit *ipso*-alkylation since transmetalation takes place after the extrusion of NBE. Therefore, modification of alkylating reagents themselves would be a more practical strategy to realize *ipso*-alkylation terminated reaction.

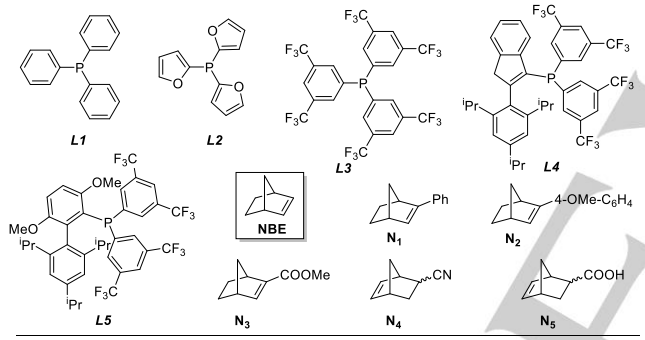
Recently, organogermanium nucleophiles[17-18] have received increasing attentions due to their balanced reactivity and stability in cross-coupling and environmentally friendliness. We found out that alkyl carbagermatranes (alkyl-***Ge***) were capable of realizing transmetalation with high efficiency.[17a] Hence, we envisioned that using alkyl-***Ge*** as *ipso*-terminating

reagents would help overcome the aforementioned challenges. We began with a classic model Catellani reaction using aryl iodide **1a**, alkyl iodide **2a** and *beta*-H containing alkyl-***Ge*** **3a** aiming at realizing *ortho*/*ipso*-dialkylation of aryl ring. Meanwhile alkyl-$B(OH)_2$ was also tested for comparison.[19]

Table 1. Reaction conditions optimization[a]



Entry	Ligand	[Pd]	N	4a/%	4a'/%	4a''/%
1	***L1***	$Pd(OAc)_2$	**NBE**	15 (10)	n.d. (n.d.)	32 (26)
2	***L2***	$Pd(OAc)_2$	**NBE**	55 (12)	n.d. (n.d.)	14 (20)
3	***L3***	$Pd(OAc)_2$	**NBE**	75 (10)	n.d. (n.d)	trace (16)
4	***L4***	$Pd(OAc)_2$	**NBE**	trace (trace)	trace (n.d.)	trace (7)
5	***L5***	$Pd(OAc)_2$	**NBE**	n.d. (trace)	n.d. (n.d.)	trace (n.d.)
6	***L3***	$Pd_2(dba)_3$	**NBE**	78	n.d.	trace
7	***L3***	$Pd(CH_3CN)_2Cl_2$	**NBE**	81	n.d.	trace
8	***L3***	$PdBr_2$	**NBE**	85	n.d.	trace
9	***L3***	$PdBr_2$	$\mathbf{N_1}$	n.d.	47	n.d.
10	***L3***	$PdBr_2$	$\mathbf{N_2}$	n.d.	57	n.d.
11	***L3***	$PdBr_2$	$\mathbf{N_3}$	33	19	trace
12	***L3***	$PdBr_2$	$\mathbf{N_4}$	80	trace	trace
13	***L3***	$PdBr_2$	$\mathbf{N_5}$	63	n.d.	trace



[a] Yields were determined by GC analysis using ^{n}hexadecane as internal standard. Reaction conditions: 0.1 mmol **1a**, 0.1 mmol **2a**, 0.2 mmol **3a**, 0.005 mmol [Pd], 0.01 mmol ligand, 0.2 mmol **N**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours. Yield of using ^{n}hexyl-$B(OH)_2$ instead of ^{n}hexyl-***Ge*** was given in the parenthesis.

Initially we tried the reaction conditions of Lautens',[9] and *ipso*-hydrogenation terminated product **4a''** was the major one along with target dialkylation product **4a** as minor one (15% for alkyl-***Ge*** and 10% for alkyl-$B(OH)_2$, Entry 1, Table 1)**.** We proposed that ligand effect would have predominant impact on the alkylation at *ipso* position. Therefore, a few electron-deficient ligands were screened. Indeed, for the case of alkyl-***Ge***, the yield of **4a** was improved remarkably using ***L2*** and ***L3*** (Entry 2-3)**,** which were less effective in direct cross-coupling reaction of alkyl-***Ge***.[17a] Especially, **4a** was obtained in 75% yield with *ipso* hydrogenated product **4a''** greatly suppressed using ***L3***. ***L4***[17a] and ***L5***[20]**,** which were proved efficient in alkyl carbatranes cross-coupling reactions, however, barely gave any dialkylation products (Entry 4-5), suggesting that the presence of bulky ^{n}Bu group at *ortho* position before the transmetalation of alkyl-***Ge*** should be credited for. As for the case of alkyl-$B(OH)_2$, ***L2***-***L5*** failed to improve the yield of **4a** and **4a''** was still found to be the major product. With the optimal ligand ***L3*** found, more conditions were tested using alkyl-***Ge***. Changing Pd source also helped improve the yield while $PdBr_2$ was able to give satisfying 85% yield (Entry 8). In addition, some NBE derivatives[21] were also evaluated yet did not prevail over the simplest NBE (Entry 9-13).

With the optimized reaction condition in hand, the scope of *ipso*/*ortho*-dialkylation protocol was investigated. We first examined the scope of aryl iodides (Figure 1A). Electron-rich 1-iodo-2-methoxybenzene, 1-Iodonaphthalene and 1-iodo-2,3-dimethylbenzene were smoothly converted to dialkylation products with good yields (**4b**-**d**). Meanwhile, electron-poor aryl iodides gave lower yields (**4j**, **4k**). Pyridine ring (**4f**) was compatible to give 74% yield. *Tert*-butyldimethylsilyl-protected benzyl alcohol (**4e**) and trifluoromethoxyl group (**4g**) were also tolerated in moderate yield. Not only Cl-bearing aryl ring (**4h**), but also Br-bearing one (**4i**) was successfully tolerated. It's noted that by subjecting *ortho* unsubstituted 1-ethyl-4-iodobenzene (**1l**), Et-I and alkyl-***Ge*** **2a** to the standard condition, 48% yield of trialkylation product **4l** was obtained with 44% **2a** unreacted. Efficiency dropped dramatically with ^{n}Pr-I and ^{n}Bu-I used as *ortho* alkylating reagents, suggesting that steric hindrance of Ar-Pd(II) species has certain impact on the transmetalationof the final alkylating termination step,[22] which is in line with Catellani's finding.[7, 23] Following, the scope of alkyl iodides was inspected (Figure 1B). 1-iodo-4-phenyl-butane and even longer 1-iodododecane were readily converted to dialkylation product with excellent yields (**4o**-**p**). Protected alcohol (**4q**), alkene (**4r**), ester (**4s**) and ketone (**4u**) were tolerated to give good yields. Notably, unprotected alcohol was also compatible albeit giving a lower yield (**4t**). It's noteworthy that while 1-chloro-4-(3-iodopropoxy)benzene was converted to dialkylation product in 73% yield (**4v**), its bromide analog gave slightly lower 62% yield. In addition, amide-containing (**4w**-**x**) alkyl iodides was also tolerated. With respect of the scope of alkyl-***Ge***, a variety of funtionalized alkyl-***Ge*** were tested (Figure 1C). Ethyl, benzyl and 3-phenylpropanyl-***Ge*** were converted to dialkylation products with good yields (**4y**-**aa**). Acetal (**4ab**), ester (**4ae**) and amide-containing (**4af**) alkyl-***Ge*** were also proved to be excellent *ipso* terminating partners. Notably, **4ac** and **4ad** were readily obtained in good yields with Cl or Br atom preserved. We next investigated the tolerance of boron-containing substrates (Figure 1D). To our surprise, even in the presence of Cs_2CO_3, a commonly used base for Suzuki cross-coupling reactions, not only boronic acid pinacol ester (Bpin), but naked boronic acids were well tolerated to give boron-contaning dialkylation products in moderate to good yields (**4ag**-**an**).

To demonstrate the utility of this alkylation terminated protocol, modification of drugs and natural products derivatives was performed (Figure 2). Vitamin E and estrone-derived aryl iodides were converted successfully to **4ao** and **4as** with 61% and 77% yields respectively. Jasmonic acid (**4ap**), indomethacin (**4aq**) and linoleic acid-derived alkyl-***Ge***[24] (**4ar**) were also competent terminating partners giving corresponding modified drug and natural products with good yields. At last, fructose-derived alkyl iodide was able to give dialkylation product **4at** in 65% yield.

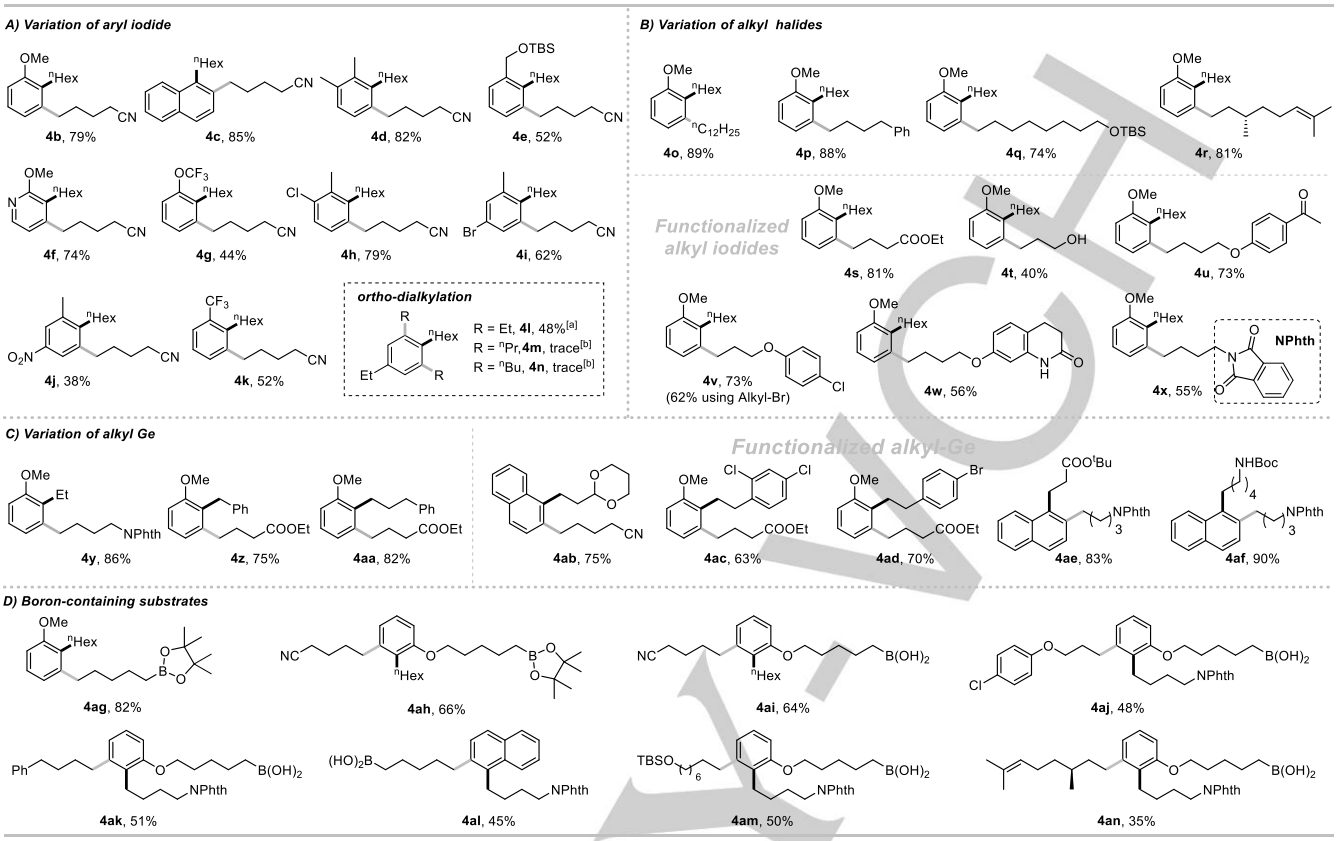


Figure 1. Scope of aryl iodides, alkyl iodides, alkyl-***Ge*** and boron-containing substrates. Yields were determined by isolation unless otherwise noted. Reaction conditions: 0.1 mmol aryl iodides **1**, 0.1 mmol alkyl-***Ge* 2**, 0.2 mmol alkyl electrophiles **3**, 0.005 mmol $PdBr_2$, 0.01 mmol ***L3***, 0.2 mmol **NBE**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours. [a] Yields were determined by GC analysis using *n*hexadecane as internal standard, 4.0 equivalent of alkyl electrophiles was used. [b] trace product was detected by TLC, 4.0 equivalent of alkyl electrophiles was used.

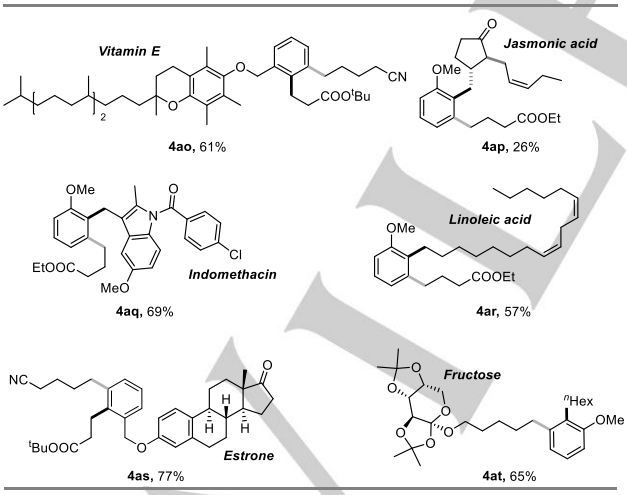


Figure 2. Modification of drugs and natural products derivatives. Yields were determined by isolation. Reaction conditions: 0.1 mmol aryl iodides **1**, 0.1 mmol alkyl-***Ge* 2**, 0.2 mmol alkyl electrophiles **3**, 0.005 mmol $PdBr_2$, 0.01 mmol **L3**, 0.2 mmol **NBE**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours.

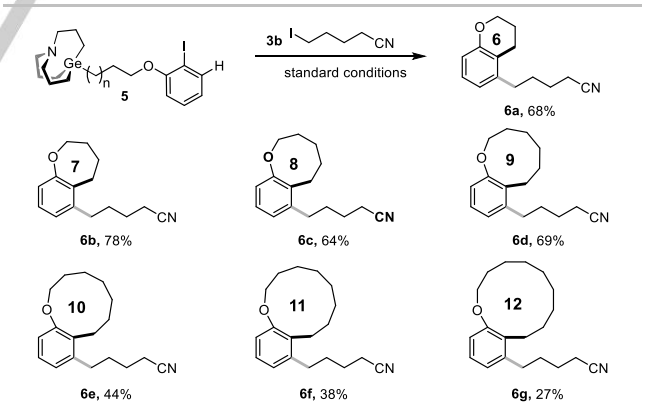


Figure 3. Intramolecular cyclization. Yields were determined by isolation. Reaction conditions: 0.1 mmol **5**, 0.2 mmol **3b**, 0.005 mmol $PdBr_2$, 0.01 mmol ***L3***, 0.2 mmol **NBE**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours.

We previously established a method to synthesize aryl iodide-incorporated alkyl-***Ge*** through decarboxylative carbagermatranation,[24] which enables us to realize intramolecular dialkylation Catellani reaction (Figure 3). With an array of precursor **5** in hand, intramolecular cyclization was performed. **6a** and **6b** were obtained in good yields while

medium ring **6c** and **6d** shown no difference in yields in general. Noticeable decline in yield was observed when the size of ring was increased to 10/11-member (**6e**-**f**) or even larger (**6g**). It needs to be pointed out that all intramolecular cyclization was performed in standard condition without diluted (0.2 M), suggesting the high efficiency of alkyl-***Ge*** as *ipso* terminating reagents.

In addition, it was found that aryl electrophiles also worked well for *ortho*-arylation in this protocol. *Ortho*-arylation/*ipso*-alkylation products were obtained with moderate to good yields (Figure 4), which further expands the paradigm of this method.

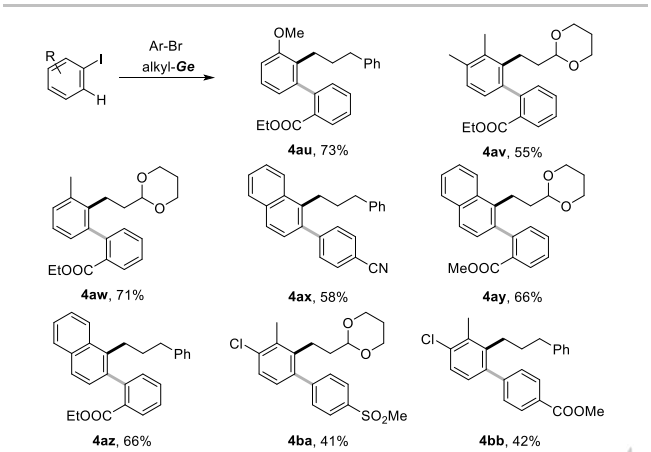
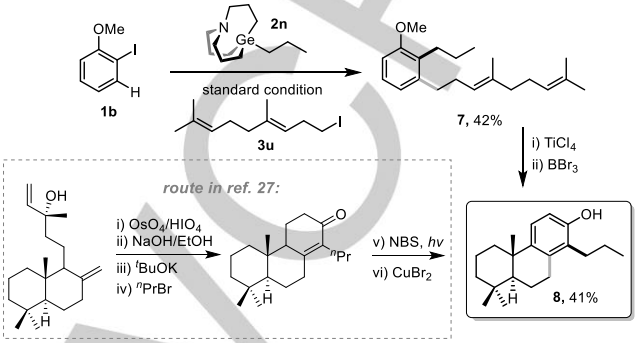


Figure 4. Scope of *ortho*-arylation. Yields were determined by isolation. Reaction conditions: 0.1 mmol aryl iodides **1**, 0.1 mmol alkyl-***Ge* 2**, 0.2 mmol aryl electrophiles **3**, 0.005 mmol $PdBr_2$, 0.01 mmol **L3**, 0.2 mmol **NBE**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours.

Regarding the aspect of mechanism, Deuterium label experiments were performed. Both paralleled and competitive deuterium label experiment gave low KIE value (see SI, Scheme S1-S2), suggesting that *ortho* C-H activation was partially included in rate-determining step, which agreed with previous researches.[19b, 25] Monitoring of reaction progress revealed that transmentalation of alkyl nucleophiles is crucial to this dialkylation strategy and also elxpained why alkyl-***Ge*** worked better that alkyl boronic acids (see more dicussion in SI*, Section 5*).[26]

At last, Catellani reaction has unique advantage in the synthesis of complex molecule, and we believe our dialkylation protocol will bring more convenience to the synthesis. Totarol is a natural terpene isolated from *Podocarpus totara* of New Zealand that exhibit antibacterial activity. Previous studies reveal that altering substituent at *ortho* position to OH group in Totarol helps regulate its lipophilicity without compromising its antibacterial activity.[27] However, previous methods for the synthesis of its derivatives are tedious. By our protocol, precursor polyenes **7** was synthesized from 1-iodo-2-methoxybenzene, ^{n}Pr-***Ge*** and homogeranyl iodide[28] **3u** in one step (Scheme 3). Following $TiCl_4$-mediated polycyclization[29] and demethylation by BBr_3 was able to give ^{n}Pr analog of Totarol **8** in 41% yield. The NMR data of analog **8** is consistent with reported literature.[27] and our synthetic route is much more simplified. Limited by the commercial source of $SbCl_5$ and the ligand, enantioselective polycyclization of **7** was not performed but already proved effectively feasible by Corey's group.[30] Theoretically, dialkylation product could be obtained by hydrogenation of Heck-terminated Catellani products. However, no Heck-type terminated Catellani reaction using propylene as terminating reagents was reported by far. Most of all, C-C double bond in homogeranyl group (**7**) may not survive from the subsequent hydrogenation..



Scheme 3. Simplified synthesis of bioactive molecule. Reaction conditions: *step 1*: 0.1 mmol **1b**, 0.1 mmol **2n**, 0.2 mmol **3u**, 0.005 mmol $PdBr_2$, 0.01 mmol ***L3***, 0.2 mmol **NBE**, 0.2 mmol Cs_2CO_3, 0.5 mL CH_3CN, 100 °C, 14 hours; *step 2*: i) 0.14 mmol **7**, 0.14 mmol $TiCl_4$, 0.6 mL DCM, RT, 2 days; ii) 0.3 mmol BBr_3, RT, 2 hours. Yields were determined by isolation.

In conclusion, dialkylation of aromatic rings was realized by Pd/NBE cooperative catalysis using alkyl carbagermatranes as alkylation terminating reagents. The scope of aryl iodides, alkyl/aryl halides and alkyl carbagermatranes were investigated. This protocol of dialkylation was compatible with alkyl boronic acid and able to construct medium rings by intramolecular cyclization. Its practicability was further demonstrated by modification of drugs and natural products derivatives and the simplified synthesis of bioactive molecule. Our study extends the scope of Catellani reaction to a new dimension with alkylating termination, and mechanism study is helpful for inspiring further exploitation of using other alky nucleophiles in Catellani reactions.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Catellani reaction • Carbagermatrane • *ipso*-alkylation • Organogermanium

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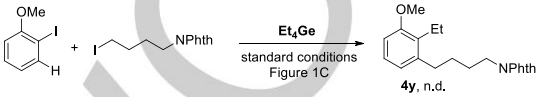
[26] Using tetraethylgermanium instead of ethyl carbagermatrane, no target product was detected, which further highlights the importance of the nucleophilic nature of the nucleophiles.



4y, n.d.

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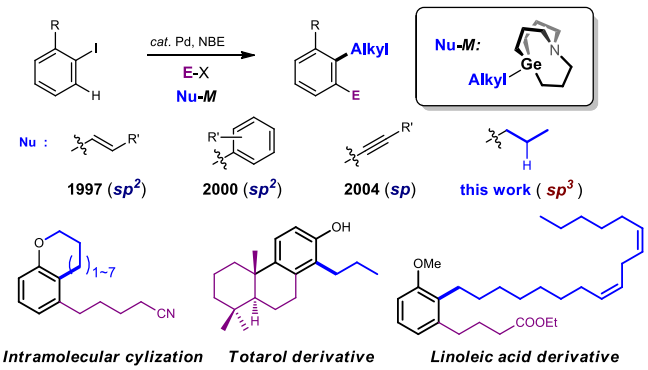

Alkylation-terminated Catellani reaction has not been well-executed in a very long time mainly due to the significant challenge of the transmetalation of beta-H incorporated alkyl groups onto the steric hindered aryl-Pd(II) intermediate. Herein, this challenge is overcome by using highly efficient alkyl-***Ge*** nucleophiles as terminating reagents.