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One-pot synthesis of N-heterocycles by tandem carbamoylation–oxidative bromolactamization of ω-alkenylmagnesium bromide

Yasutomo Yamamoto [a,*], Yuji Takahama [b], Misa Shimizu [a], Ai Ohara [a], Akari Miyawaki [a], Kiyoshi Tomioka [a,*]

[a] Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe 610-0395, Japan
[b] Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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ABSTRACT

An addition reaction of ω-alkenylmagnesium bromide with *p*-toluenesulfonyl isocyanate and consecutive oxidative cyclization with iodobenzene diacetate afforded brominated lactams in one-pot. An imine was also applicable to a one-pot synthesis of terminally brominated cyclic amine.

The addition reaction of nitrogen nucleophiles with a carbon–carbon multiple bond (i.e., hydroamination) is a very powerful carbon–nitrogen bond forming reaction.[1] Our studies have been aimed at chiral diether-mediated asymmetric conjugate addition reactions of lithium amides with enoates.[2] An intramolecular version of the amination reaction is an effective process for the synthesis of nitrogen-containing heterocycles, and we previously reported a chiral bisoxazoline–lithium amide-catalyzed asymmetric intramolecular hydroamination of aminoalkene.[3] In these reactions, in situ-generated highly reactive lithium amides were used as nitrogen nucleophiles to react with a C=C double bond, giving the aminolithiation product. An addition reaction of organometallic reagents with a C=N double bond is an alternative protocol to prepare nucleophilic metal amide, whose reaction with an intramolecular carbon–carbon multiple bond allows for the synthesis of nitrogen-containing heterocycles in one pot.[4] This approach is highly advantageous in that stepwise synthesis of the cyclization precursor for heterocycles is unnecessary. Herein we report a one-pot addition reaction of ω-alkenylmagnesium bromide with a C=N double bond–bromolactamization tandem reaction by the oxidation of an anionic intermediate as a key step.

A reaction of 3-butenylmagnesium bromide **1a** with *N*-tosylisocyanate **2** in THF for 0.5 h at 0 °C gave the corresponding magnesium amide **3a**, which no longer reacted at this stage probably due to the low nucleophilicity of metal amide toward olefin, and amide **5a** was obtained quantitatively after quenching with aqueous ammonium chloride (scheme 1). Oxidation of anionic species to radical or cationic species is an important umpolung methodology for changing the reactivity of anionic intermediates, and it is potentially useful for combination with anionic cascade reactions.[5] In fact, in situ oxidation of **3a** with 2 equiv of $PhI(OAc)_2$ in dichloroethane (DCE) gave bromolactam **4a** in 55% yield and **5a** in 40% yield.[4] Increasing the amount of $PhI(OAc)_2$ to 4 equiv gave **4a** in 83% yield (Scheme 1 and Table 1, entries 1 and 2). The same transformation to **4a** could be achieved with the addition of 2 equiv bromine or NBS to a solution of **3a** as a Br^+ source.[6]

Bromolactamization of amide **5a** itself did not proceed at all with NBS or bromine/$NaHCO_3$, which resulted in the recovery of **5a** as shown in Scheme 2. On the other hand, once **5a** was converted to the corresponding lithium amide **6a** with *n*-BuLi, subsequent treatment with bromine gave cyclized **4a** in 76% yield. These results clearly show that the cyclization step requires the activation of nitrogen nucleophiles as magnesium- or lithium amides, such as **3a** or **6a**, and the one-pot process, in which reaction of **1a** with **2** gave 'activated' magnesium amide **3a**, has an advantage over the stepwise process.

The reaction conditions were optimized by the examination of various oxidants (Table 1). The powerful hypervalent iodine oxidant $PhI(OCOCF_3)_2$ afforded **4a** in moderate (65%) yield (entry 3). CAN and DDQ gave **4a** in 45% and 48% yield, respectively (entries

* Corresponding authors. Tel.: +81 774 65 8676; fax: +81 774 65 8658.
E-mail addresses: yayamamo@dwc.doshisha.ac.jp (Y. Yamamoto), tomioka@pharm.kyoto-u.ac.jp (K. Tomioka).

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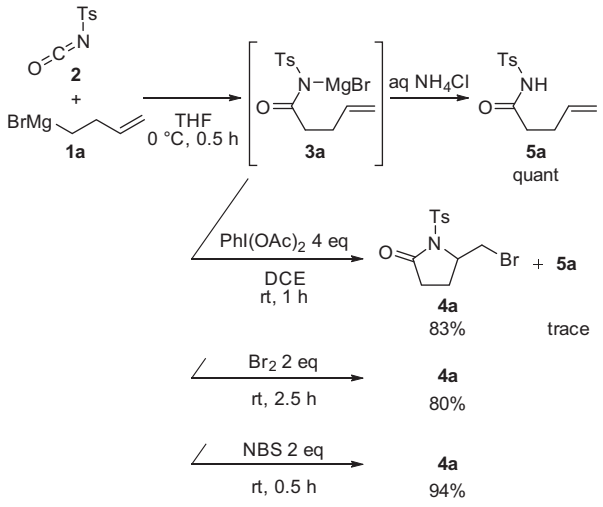
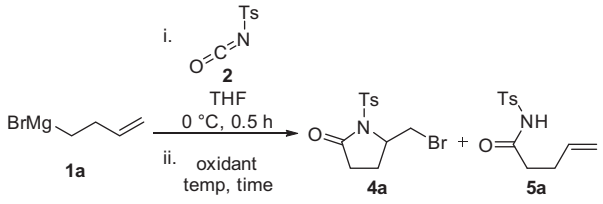


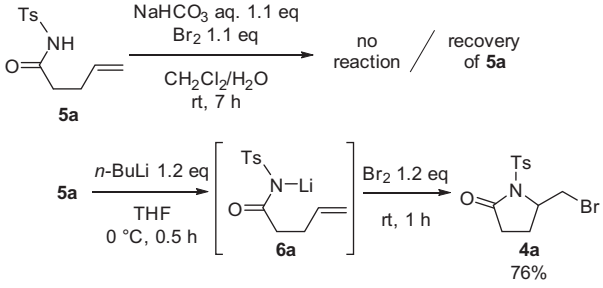
Scheme 1. Tandem carbamoylation–oxidative bromolactamization of 3-butenylmagnesium bromide **1a** with isocyanate **2**.

Table 1
Screening of oxidants



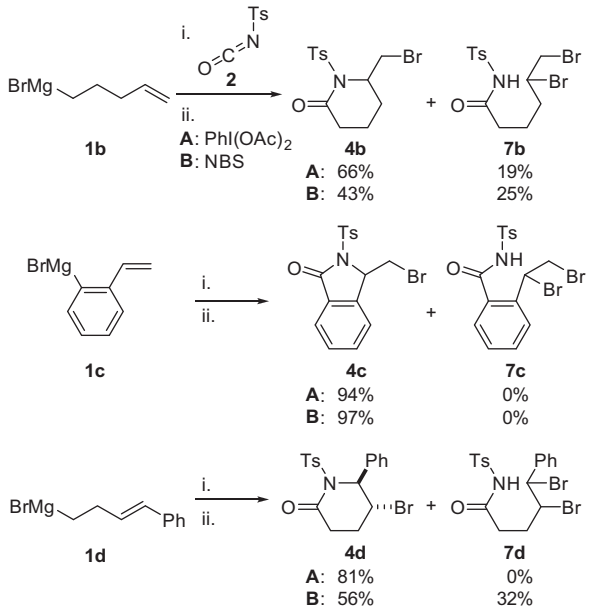
Entry	Oxidant/equiv	Temp (°C)	Time (h)	**4a** % Yield	**5a** % Yield
1[a]	$PhI(OAc)_2$/2	rt	1	55	40
2[a]	$PhI(OAc)_2$/4	rt	1	83	Trace
3[b]	$PhI(OCOCF_3)_2$/4	rt	1	65	27
4[b]	CAN/4	rt	1	45	20
5	DDQ/4	rt	1	48	38
6	aq H_2O_2/4	rt	3	2	69
7	H_2O_2–urea/2	rt	2	18	68
8	H_2O_2–$(Ph_3PO)_2$/4	rt	1	42	45
9	*m*CPBA/1.1	0	1	64	30
10	*m*CPBA/5	0	2	58	35
11	$(PhCO_2)_2$/4	rt	1	63	23

[a] DCE was used as a co-solvent in the oxidation step.
[b] MeCN was used as a co-solvent in the oxidation step.

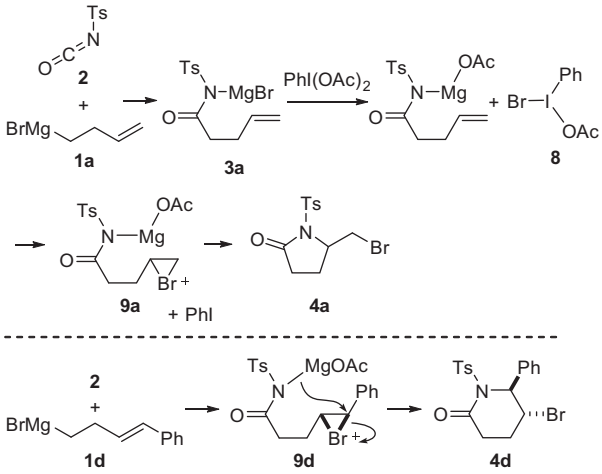


Scheme 2. Bromolactamization of **5a**.

4 and 5). An aqueous solution of H_2O_2 was incompatible due to the protonation of magnesium amide intermediate **3a** by water to give **5a**, whose subsequent cyclization did not proceed (entry 6 and Scheme 2). Anhydrous hydrogen peroxide, H_2O_2–urea, and H_2O_2–$(Ph_3PO)_2$ complex, led to better results than aqueous H_2O_2, but



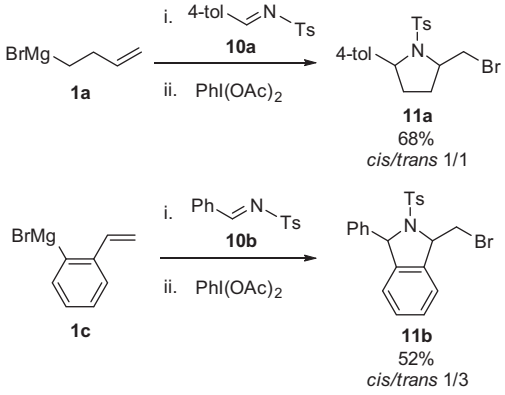
Scheme 3. Carbamoylation–oxidative bromolactamization of Grignard reagents **1b–d**.



Scheme 4. Plausible reaction mechanism.

the yield remained only moderate (entries 7 and 8). *m*CPBA at 1.1 equiv afforded **4a** in 64% yield, but increasing the amount of *m*CPBA to 5 equiv did not improve the yield (entries 9 and 10). Benzoyl peroxide, which does not have acidic protons, gave a yield (63%) similar to that of *m*CPBA (entry 11). Thus, oxidative bromolactamization was mediated by various types of oxidants, and 4 equiv of $PhI(OAc)_2$ was optimal.

The applicability of other Grignard reagents was also examined (Scheme 3). Carbamoylation of 4-pentylmagnesiumbromide **1b** with **2**, followed by $PhI(OAc)_2$-mediated cyclization (method A) gave the 6-*exo*-cyclization product **4b** and dibromide **7b** in 66% and 19% yield, respectively. The NBS-mediated protocol (method B) afforded a decreased yield (43%) of **4b** and an increased yield (25%) of undesired **7b**. Styryl magnesium bromide **1c** gave five-membered lactam **4c** in excellent yield (94% with method A and 97% with method B). When Grignard reagent **1d** having (*E*)-olefin was used, *trans*-6-*endo* cyclized product **4d** was obtained in 81% yield by method A. Method B gave a considerable amount of non-cyclized, dibrominated product **7d** (32%) as well as cyclized



Scheme 5. A one-pot synthesis of cyclic amine **11** using Grignard reagent **1** and imine **10**.

product **4d** (56%). Oxidative bromolactamization with $PhI(OAc)_2$ suppressed the formation of dibrominated product **7b** and **7d**.[7]

The putative reaction pathway is shown in Scheme 4. Reaction of the Grignard reagent with isocyanate gave magnesium amide **3a**, and subsequent treatment with $PhI(OAc)_2$ generated bromoiodinane **8**, which acted as a Br^+ equivalent to give bromonium **9a**,[8,9] and finally nucleophilic opening gave bromolactam **4a**.[10,11] The use of Grignard reagent **1d** led to an intramolecular S_N2-type opening reaction of amide with bromonium of intermediate **9d**, which proceeded at the positively charged benzyl position and resulted in the formation of *trans*-6-*endo* cyclized product **4d**, suggesting a Br^+ reaction instead of a radical reaction.[12] The characteristic feature of this reaction is that both alkyl group and bromide of Grignard reagent were incorporated in the reaction product.

This one-pot process was also applicable to the synthesis of cyclic amine by the reaction of imine in place of isocyanate (Scheme 5). The reaction of Grignard reagent **1a**, **1c** with *N*-tosylimine **10a**, **10b** followed by $PhI(OAc)_2$ oxidation gave cyclic sulfonamide **11a**, **11b** in 68% and 52% yield, respectively.

In conclusion, a one-pot synthesis of bromolactams was achieved by a tandem reaction of ω-alkenylmagnesium bromide with C=N double bond–oxidative bromolactamization. The methodology could be applied to the synthesis of brominated cyclic amine using imines as electrophiles.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and characterization data of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.002.

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