Electrophile-triggered Assembly of Metal Enamides and Allyl Grignard Reagent in One Pot. Novel Nucleophilic Double Allylation of Azadienes

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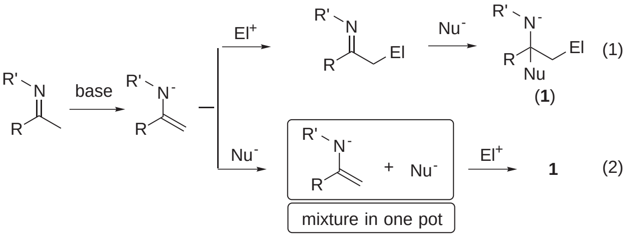
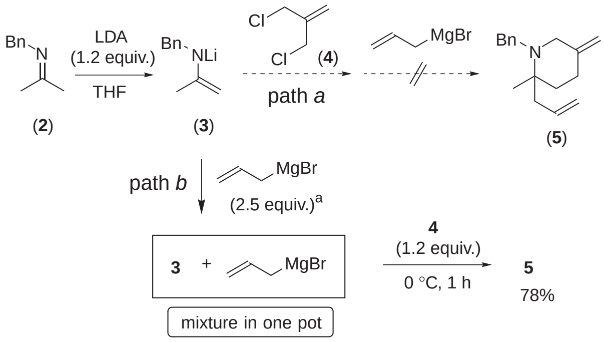
When an electrophile (H^+ or an alkyl halide) was added to a mixture of 1-aryl-2-aza-1,3-butadiene and allyl Grignard reagent, selective assembly of the azadiene, nucleophiles, and an electrophile took place to give α,α'-diallylated amine in one pot.

Imines play a pivotal role in the synthesis of organic compounds containing nitrogen.[1] Eq 1 in Scheme 1 shows their standard utility, involving deprotonation followed by the reaction with an electrophile (El^+) and then with a nucleophile (Nu^-) to give product **1**.[2] Herein, we report an alternative and anomalous case where the order of the addition of El^+ and Nu^- could be reversed, still giving the same product **1**, as formulated in eq 2. The latter phenomenon involves a selective assembly of two nucleophiles and an electrophile in one pot, and led us to develop a new multi-component coupling process based on azadienes.



Scheme 1. Formulation of synthetic reactions of imines.

During the course of our study on nitrogen heterocycles, we needed to prepare piperidine derivative **5**. However, in our hands, attempted reactions of imine **2** with LDA (to generate lithium enamide **3**[2]), bis-allylic chloride **4**, and allyl Grignard reagent under various reaction conditions according to the standard protocol shown in eq 1 did not give the desired product **5**, but gave a mixture of messy products (path *a* in Scheme 2).[3] Contrary to this unsuccessful outcome, when we happened to add bis-allylic chloride **4** to a pre-formed mixture of lithium enamide **3** and allyl Grignard reagent, the desired product **5** was obtained in good yield (path *b*, hence, eq 2 in Scheme 1). It should be emphasized that the success of path *b* was not a priori expected, because the feasible random reactions between two kinds of nucleophiles and an electrophile in the same reaction vessel most likely block the controlled assembly of **3**, **4**, and the Grignard reagent. The electrophile is not limited to dichloride **4**, but also is valid for simple ones such as allyl bromide (1.2 equiv.), MeI (5 equiv. for dimethylation), or even D^+ (excess D_2O) affording the desired products **6** (80%), **7** (48%), or **8** (74%)[4] (Chart 1). Thus, these reactions proved to be a dependable (and, in certain cases, indispensable) modification to the standard transformation illustrated in eq 1.



Scheme 2. Unsuccessful and successful paths *a* and *b*. [a]1.2 out of 2.5 equiv. of this Grignard reagent is allotted for deprotonation of $(i\text{-Pr})_2NH$.

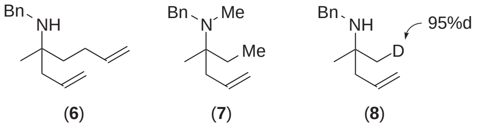
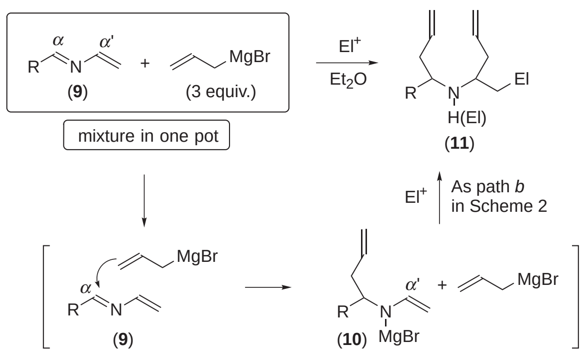


Chart 1.

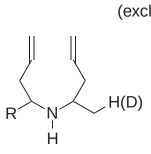
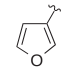
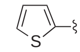
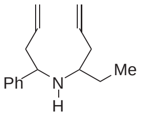
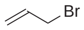
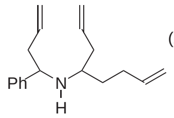
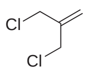
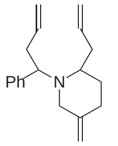
The selective assembly of metal enamide and allyl Grignard reagent triggered by an electrophile disclosed above brought us a step closer to developing a new multi-component coupling process based on azadienes. When an electrophile was added to a mixture of azadiene **9**[5] and allyl Grignard reagent, double allylation of **9** together with the uptake of the electrophile took place to give product **11** in one pot (Scheme 3). The reaction apparently consists of the first Grignard addition to the imine portion of **9** (α position) to generate magnesium enamide **10**,[6] followed by the second allylation at the α' position initiated by the addition of an electrophile as precedented by path *b* in Scheme 2. This type of double alkylation of azadienes **9** has not been reported.[7] Table 1[8] shows that a variety of azadienes **12**–**17** are good substrates for this reaction to give desired products **18**–**23** after protonation or deuteration (Entries 1–6). The heteroaromatic portion in **22** and **23** may be useful for further synthetic manipulation including the conversion to an aliphatic carbon framework.[9] More importantly, the double α- and α'-allylation of azadiene **12** induced by an alkyl halide gave products **24**–**26** (Entries 7–9), achieving a four-component coupling reaction that is otherwise difficult to execute.

Synthetic utility of two allyl groups simultaneously introduced by the above transformation was demonstrated as follows. The ring-closing metathesis (RCM) of **27** derived **18** (Table 1, Entry 1) under ruthenium catalysis[10] readily furnished seven-membered aza-cycle **28** (or **29** after deprotection) as shown in eq 3.[11]

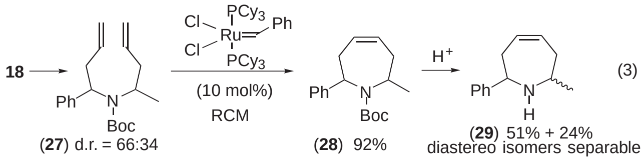


Scheme 3. Double allylation of azadienes **9**.

Table 1. Results of electrophile-triggered double allylation of azadienes according to Scheme 3

Entry	R in azadiene **9**		El$^+$ (equiv.)	Product^a	Yield/%^{b}
1	Ph-	(**12**)	D$^+$ (excess)^c		(**18**-*d*) 52 (exclusively deuterated)
2	*p*-BrC$_6$H$_4$-	(**13**)	H$^+$ (excess)^d		(**19**) 62
3	*p*-ClC$_6$H$_4$-	(**14**)	"		(**20**) 58
4	*p*-(MeO)C$_6$H$_4$-	(**15**)	"		(**21**) 44
5		(**16**)	"		(**22**) 56
6		(**17**)	"		(**23**) 51
7	Ph-	(**12**)	MeI (1.5)		(**24**) 80
8	Ph-	(**12**)	 (1.5)		(**25**) 54
9	Ph-	(**12**)	 (**4**) (5)		(**26**) 68

^{a}Diastereomeric ratio of the products falls within a range of 50:50–67:33. Stereochemical assignments for major and minor isomers have not yet been done. ^{b}Isolated yields. ^{c}D$_2$O was used. ^{d}H$_2$O was used.



(**27**) d.r. = 66:34 (**28**) 92% (**29**) 51% + 24% diastereo isomers separable

In conclusion, a one-pot four-component coupling process based on a novel double α- and α'-allylation of azadienes with concomitant incorporation of an electrophile has been achieved. The success of this process is based on the anomalous coupling of metal enamides and allyl Grignard reagent triggered by an electrophile.

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This article is dedicated to Dr. Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

1 *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon Press, Oxford, **1991**, Vol. 1–7.

2 S. Mangelinckx, N. Giubellina, N. De Kimpe, *Chem. Rev.* **2004**, *104*, 2353; J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983**, 517.

3 Incompatibility of the intermediate allylated imine with the reaction media or allyl Grignard reagent may account for the failure of path *a*.

4 As the pK_a values of imine **2** and propene, conjugated acids of lithium enamide **3** and allyl Grignard reagent, are estimated to be 30–35 and 38, respectively (H. O. House, *Modern Synthetic Reactions,* 2nd ed., Benjamin, California, **1972**, pp. 494–495), selective deuteration (protonation) to metal enamide **3** in the presence of the more basic allylic carbanion during the production of **8** is a noticeable observation. For a review on the reactivity of poly-anionic systems, see: C. M. Thompson, D. L. C. Green, *Tetrahedron* **1991**, *47*, 4223.

5 These stereochemically defined azadienes were prepared as reported. H. Böhme, A. Ingendoh, *Chem. Ber.* **1979**, *112*, 1297; L. L. Nikogosyan, K. A. Nersesyan, T. Y. Satina, G. A. Panosyan, M. G. Indzhikyan, *Zh. Org. Khim.* **1989**, *25*, 749; *J. Org. Chem. USSR* **1989**, 671.

6 As an attempted stoichiometric addition of the Grignard reagent to the imine portion of azadiene **9** did not reach completion, the excess use of the Grignard reagent was anyway inevitable at this step.

7 For a review on reactions of azadienes, see: S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379.

8 Typical procedure for *N*-(1-ethyl-3-butenyl)-*N*-(1-phenyl-3-butenyl)amine as a 50:50 mixture of diastereoisomers (**24**, Entry 7, Table 1). To a solution of *N*-benzylidene-*N*-vinylamine (**12**) (52.4 mg, 0.400 mmol) in 20 mL of ether was added 1.0 M allylmagnesium bromide in ether (1.20 mL, 1.20 mmol) at −40 °C under argon. After the mixture was stirred at −30 °C for 2 h, iodomethane (0.037 mL, 0.600 mmol) was added and the reaction mixture was allowed to warm to room temperature. After being stirred at this temperature for 1 h, the reaction was terminated by the addition of an aqueous saturated NaCl solution (1.0 mL). The organic products were extracted with ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo to give a crude oil, ^{1}H NMR analysis of which revealed the diastereomeric ratio to be 50:50. The crude sample was chromatographed on silica gel to afford the title compound (73.3 mg, 80%) of the same isomeric composition as an oil.

9 *Comprehensive Heterocyclic Chemistry*, ed. by A. R. Katritzky, C. W. Rees, Pergamon Press, Oxford, **1984**, Vol. 4.

10 G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856; R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446.

11 For a recent synthesis of 7-membered azacycles by RCM, see: Q. Yao, Y. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 74, and references cited therein.