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Zinc-Mediated Highly α-Regioselective Prenylation of Imines with Prenyl Bromide

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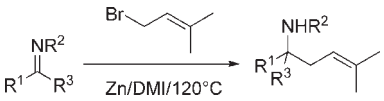
ABSTRACT



R^1 = aryl, alkyl; R^2 = aryl, alkyl; R^3 = H, Me

A highly α-regioselective prenylation of imines has been successfully developed. The efficiency of this approach is confirmed by a wide range of imines including *N*- and *C*-aryl aldimines, *N*-alkyl aldimines, *C*-alkyl aldimines, and *N*- and *C*-aryl ketimines. The approach uses prenyl bromide as the prenyl source and inexpensive and convenient zinc as the mediator as well as environmentally benign 1,3-dimethyl-2-imidazolidinone (DMI) as the solvent.

Allylation is one of the most valuable and important reactions for the construction of C−C bonds.[1] Regioselectivity is a very important issue in allylation. Generally, highly α-regioselective allylation is difficult to achieve when α-substituted allylmetal reagents such as prenylmetal are employed.[2] However, despite the difficulty in obtaining an α-adduct, many successful examples of α-regioselective allylation of aldehydes and ketones have been reported.[3] While great progress has been made on the regioselective allylation of carbonyl compounds, very few examples have been described for their aza analogues. The difficulty is mainly ascribed to the poor electrophilicity of imines and deprotonation of imines derived from enolization.[4] In the past 15 years, only two efficient methods for the synthesis of linear homoallylic amines via allylation of imines with prenylmetals have been reported. The first α-regioselective prenylation of an imine with a prenyl halide was reported by Yamamoto in 1996.[5] Another successful α-selective addition to imines was described by Shibata in 2009.[6] However, despite the success, both methods are limited to aldimines only and are not applicable to ketimines, so the regioselectivity issue of imines is not addressed completely. On the other hand, the very few examples of α-regioselective prenylation have limited the availability of linear homoallylic amines, which have proved to be important building blocks of natural products and biologically active molecules.[7] Thus, the development of more efficient α-regioselective prenylation of imines for the facile preparation of linear homoallylic amines in high yields, which has a broader substrate scope and uses

(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(2) (a) Sinha, P.; Roy, S. *Organometallics* **2004**, *23*, 67. (b) Kaellstroem, S.; Erkkilae, A.; Pihko, P. M.; Sjoeholm, R.; Sillanpaeae, R.; Leino, R. *Synlett* **2005**, 751. (c) Moslin, R. M.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 9736. (d) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073. (e) Alcaide, B.; Almendros, P.; del Campo, T. M. *Eur. J. Org. Chem.* **2008**, 2628. (f) Millan, A.; Campana, A. G.; Bazdi, B.; Miguel, D.; Alvarez de Cienfuegos, L.; Echavarren, A. M.; Cuerva, J. M. *Chem.—Eur. J.* **2011**, *17*, 3985.

(3) (a) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710. (b) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955. (c) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130. (d) Estevez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; Garcia-Ruiz, J. M.; Robles, R.; Gansauer, A.; Cuerva, J. M.; Oltra, J. *Chem.—Eur. J.* **2009**, *15*, 2774. (e) Zhao, L. M.; Jin, H. S.; Wan, L. J.; Zhang, L. M. *J. Org. Chem.* **2011**, *76*, 1831.

(4) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(5) Yanagisawa, A.; Ogasawara, K.; Yasue, K.; Yamamoto, H. *Chem. Commun.* **1996**, 367.

(6) Shibata, I.; Miyamoto, S.; Tsunoi, S.; Sakamoto, K.; Baba, A. *Eur. J. Org. Chem.* **2009**, 3508.

(7) (a) van Lierop, B. J.; Jackson, W. R.; Robinson, A. J. *Tetrahedron* **2010**, *66*, 5357. (b) Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150. (c) Smith, A. B., III; Wang, W.; Charnley, A. K.; Carroll, P. J.; Kenesky, C. S.; Hirschmann, R. *Org. Lett.* **2010**, *12*, 2990. (d) Datta, S.; Kazmaier, U. *Org. Biomol. Chem.* **2011**, *9*, 872.

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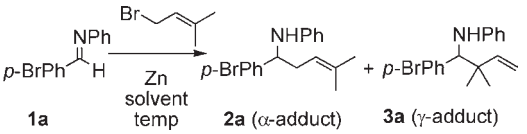
more convenient and cheaper reagents, would be of great importance.

Recently, our group reported a highly α-regioselective zinc-mediated prenylation of aldehydes and ketones.[3e] The reaction is applicable to a wide range of carbonyls and is convenient using commercially available and cheap metal. In light of this work, we wondered whether the method could be expanded to the prenylation of imines. Herein, we report a facile and general zinc-mediated method for the prenylation of aldimines and ketimines with high α-regioselectivity in DMI to afford linear homoallylic amines in good to excellent yields. The results presented show that this approach is quite reliable and very general. Remarkably, we have been able to expand the reaction to *N*-aliphatic aldimines and ketimines, broadening the applicability of the α-prenylation reaction.

Initially *N*-(4-bromophenyl)benzaldimine **1a** was selected as a model substrate to optimize the reaction conditions. The results are summarized in Table 1. We are pleased to find that the prenylation of the imine also exhibits highly α-regioselectivity to give the α-product **2a** in 89% yield under the same reaction conditions previously applied in the prenylation of carbonyl compounds (entry 1). Although notable efficacy was achieved for the reaction, the carcinogenic HMPA was used as the solvent. Hence, we decided to explore alternative solvents for the prenylation reaction of imines. Several solvents including tetramethylurea (TMU), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU), and DMI were tested. Among the solvents tested, DMI was found to be the most suitable solvent for the prenylation of imines to afford α-adduct **2a** exclusively in 95% yield (entry 3). A similar result was observed when DMPU was used as the solvent (97% yield, entry 2). Although both DMPU and DMI were developed as safe substitutes for the carcinogenic HMPA, DMI was a better choice than DMPU due to its lower toxicity. There have been several reports indicating that DMPU also may act as a possible chemical mutagen, and the potential carcinogenic risk of DMPU cannot be ignored.[8] In contrast, DMI is nontoxic to humans and the potential toxicological risk is extremely low. DMI was thus chosen for further investigation. The prenylation also can be carried out in other solvents such as TMU with complete α-regioselectivity, although a slightly lower product yield is obtained (entry 6). To enable the reaction to be performed under much milder conditions, we subsequently examined the reaction temperature. A decrease in the temperature to 120 °C did not affect the α-prenylation reaction efficiency (entry 4). In further lowering the temperature to 110 °C, the reaction still efficiently afforded α-addition product **2a** as the major product but with an amount of undesired γ-addition product **3a** (entry 5). These results showed that a reaction temperature of 120 °C was necessary to keep the high α-regioselectivity and also highlighted the key role of temperature in the regiocontrol of the reaction.

(8) (a) Zijlstra, J. A.; Vogel, E. W. *Mutat. Res.* **1988**, *201*, 27. (b) Lo, C. C.; Chao, P. M. *J. Chem. Ecol.* **1990**, *16*, 3245.

Table 1. Optimization of Reaction Conditions[a]

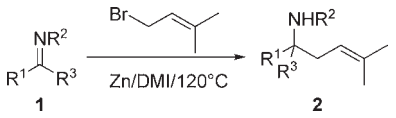


entry	solvent	temp (°C)	*t* (h)	yield (%)[b]	α/γ[c]
1	HMPA	130	12	89	>99:1
2	DMPU	130	14	97	100:0
3	DMI	130	14	95	100:0
4	DMI	120	14	96	100:0
5	DMI	110	14	68	74:26
6	TMU	130	14	89	100:0

[a] Reactions were carried out with imine (1.0 equiv), prenyl bromide (2.0 equiv), and zinc (2.5 equiv). [b] Isolated yield of **2a**. [c] Determined by GC-MS.

With optimized reaction conditions in hand, we next investigated the scope of the prenylation of imines, and the results are summarized in Table 2. A wide range of differently substituted imines derived from aromatic aldehydes and amines were investigated first. As can be seen in Table 2 (entries 1−11), linear homoallylic amines were obtained in excellent yields in all the cases. The results clearly display that a substituent on the two aromatic rings (i.e., R^1 and R^2), whether *C*-aryl- or *N*-aryl-substituted, has no significant influence on the α-prenylation reaction. Both electron-withdrawing and -donating substituents on R^1 or R^2, such as fluoride (entries 2−5), chloride (entries 6 and 7), bromide (entry 8), methoxyl (entries 9 and 10), and methyl groups (entry 11), were well tolerated in the reaction. It should be noted that the reaction allowed the use of substrates previously considered incompatible with α-prenylation. For instance, 4-methoxyphenyl-substituted imine **1j** has been reported as unreactive toward the addition of prenyltributyltin in the presence of $HfCl_4$ due to its low electrophilicity.[6] With the exception of the relatively stabilized *C*-aryl imines, the less stable *C*-heteroaryl imine such as *C*-2-thienyl imine **1m** also gave total α-regioselectivity in high yield (entry 12). Moreover, the same reactions proceeded efficiently for substrate **1n** bearing an alkyl group on R^1, providing the corresponding α-prenylation product **2n** in 82% yield (entry 13). It is sometimes difficult to handle alkyl aldimines generated from aliphatic aldehydes due to their low stability. So such substrates have scarely proved to be viable in high yields before. Further, we can also expand this reaction to new classes of imines, such as *N*-alkyl imines. When the aromatic amines were replaced by the *N*-aliphatic amines, the reaction also proceeded smoothly under the same conditions to give exclusively the corresponding α-product, albeit in slightly lower yield. For example, the *N*-*tert*-butyl imine **1o** afforded corresponding α-prenylation product **2o** in 82% yield with total α-regioselectivity (entry 14). Similarly, the use of other *N*-aliphatic imines such as *N*-benzyl

Table 2. α-Prenylation of Various Aldimines and Ketimines



entry	imine	R^1	R^2	R^3	adduct	yield (%)[a]	α/γ[b]
1	**1b**	Ph	Ph	H	**2b**	90	100:0
2	**1c**	2-FC_6H_4	Ph	H	**2c**	84	>99:1
3	**1d**	3-FC_6H_4	Ph	H	**2d**	90	>99:1
4	**1e**	4-FC_6H_4	Ph	H	**2e**	96	>99:1
5	**1f**	Ph	4-FC_6H_4	H	**2f**	90	100:0
6	**1g**	4-ClC_6H_4	Ph	H	**2g**	95	>99:1
7	**1h**	Ph	4-ClC_6H_4	H	**2h**	85	100:0
8	**1i**	Ph	4-BrC_6H_4	H	**2i**	94	100:0
9	**1j**	4-$CH_3OC_6H_4$	Ph	H	**2j**	87	100:0
10	**1k**	Ph	4-$CH_3OC_6H_4$	H	**2k**	91	>99:1
11	**1l**	4-$CH_3C_6H_4$	Ph	H	**2l**	87	>99:1
12	**1m**	2-thienyl	Ph	H	**2m**	87	100:0
13	**1n**	cyclopropyl	Ph	H	**2n**	82	100:0
14	**1o**	Ph	*tert*-butyl	H	**2o**	82	100:0
15	**1p**	Ph	$PhCH_2$	H	**2p**	70	100:0
16	**1q**	Ph	cyclohexyl	H	**2q**	61	100:0
17	**1r**	Ph	Ph	CH_3	**2r**	83	100:0
18	**1s**	4-ClC_6H_4	Ph	CH_3	**2s**	88	100:0
19	**1t**	4-$CH_3C_6H_4$	Ph	CH_3	**2t**	84	100:0
20	**1u**	4-$CH_3OC_6H_4$	Ph	CH_3	**2u**	86	100:0

[a] Isolated yield. [b] Determined by GC-MS.

imine **1p** and *N*-cyclohexyl imine **1q** also gave satisfactory α-regioselective results (entries 15 and 16). It is noteworthy that this is the first example of using *N*-aliphatic imines as the substrates in the α-prenylation of imines.

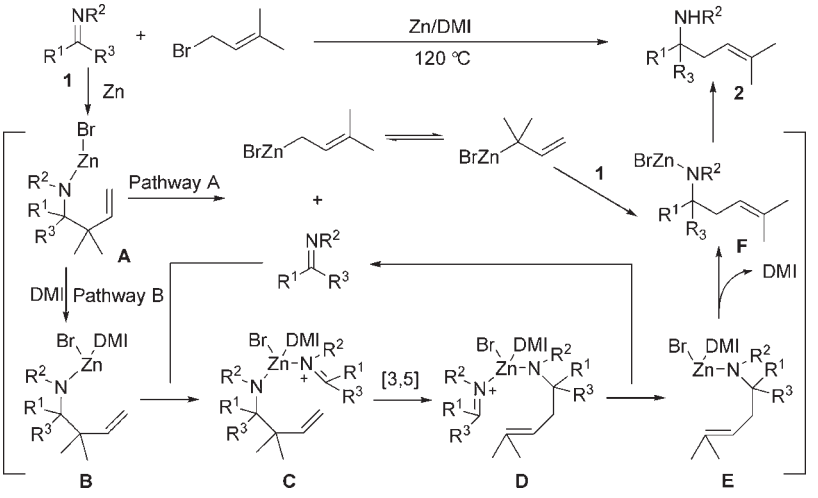
To broaden the scope of the α-prenylation reaction, the subsequent study was focused on the ketimines derived from methyl ketones. To our delight, the experiments show that this method also was very effective for the α-prenylation of various ketimines bearing electron-withdrawing (entry 18) and electron-donating groups (entries 19 and 20) at the phenyl ring in high yields. Notably, for all the substrates, the reactions afforded an α-adduct with total α-regioselectivity and no γ-adduct was observed.

Although it is impossible to establish an exact mechanism at the present time, we propose two possible pathways to explain the highly α-regioselective prenylation of imines based on our previous mechanistic study on the prenylation of carbonyls,[3e] as shown in Scheme 1. The initial step of both pathways is the formation of γ-prenylation product **A**. On the one hand, α-adducts are proposed to derive from the addition of tertiary prenylzinc generated in situ to the imine to give **F** via a six-membered cyclic transition state (path A). On the other hand, the initially formed **A** would coordinate to DMI to form complex **B**. The subsequent coordination of complex **B** to the imine results in the formation of transition state **C**, which undergoes a metallo[3,5]-sigmatropic rearrangement to afford transition state **D**. Then, complex **E** is formed from **D** by regenerating the parent imine. Finally, the dissociation of DMI from **E** liberates the ligand to deliver amido-zinc species **F** (path B).

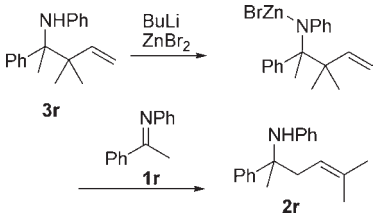
To test the proposed mechanism, an experiment involving resubjection of the γ-isomer **3r** to the reaction conditions was performed. Resubjection of the initial addition product **3r** at 120 °C in DMI in the presence of BuLi and zinc bromide led to α-isomer **2r** in 80% yield after column chromatography (Scheme 2). Although the detailed mechanism is not fully understood, our experiments make it clear that this is an equilibrium process in which the readily available kinetic γ-isomer rearranges to their less readily accessible thermodynamic α-isomer at a high temperature in DMI. At this stage, we have not yet been able to determine which pathway is correct. However, both pathways can explain why the basic solvent effects this α-prenylation reaction. In pathway A, the basicity of DMI leads to a decrease in the proportion of primary allylmetallic type and an increase of tertiary allylmetallic type.[9] In pathway B, it is quite probable that the Lewis acidity of zinc of initially formed γ-adduct **A** is enhanced by coordination with DMI. The resulting complex **B** further coordinates the imine to form the transition state **C**, followed by a [3,5]-sigmatropic shift at an elevated temperature to form the transition state **D**.

(9) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

Scheme 1. Proposed Mechanism for the α-Regioselective Prenylation of Imines



Scheme 2. A Resubjection Experiment of γ-Adduct



In conclusion, a general route to linear homoallylic amines in good to excellent yields has been developed. The reaction is highly efficient, and the scope of it is wide. Although somewhat higher temperatures are needed, this reaction is very convenient due to the use of prenyl halide as the prenyl source and inexpensive, easily obtained zinc as the mediator. Particularly noteworthy is that the reaction can be carried out in an environmentally benign solvent, which is of relevance from the viewpoint of green chemistry. To the best of our knowledge, this represents the most general and easy procedure for the synthesis of linear homoallylic amines so far. With these advantages, we believe that this new methodology may find wide application in organic chemistry.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.