Synthetic Methodology

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Characterization and Utility of N-Unsubstituted Imines Synthesized from Alkyl Azides by Ruthenium Catalysis**

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Imines have been recognized as pivotal intermediates in organic synthesis, particularly for the preparation of nitrogen-containing bioactive natural products and derivatives.[1,2] Compared with carbonyl groups, imines are more difficult to handle because of their chemically labile nature. As a result of this problem, the transformation into the amine products usually employs imines possessing a substituent on the nitrogen atom (N-substituted imines). However, from a synthetic viewpoint this protocol necessitates removal of the substituent to access the amine products [Eq. (1), Figure 1]. In this regard, the use of N-unsubstituted imines would be ideal in that the elimination step is not necessary.

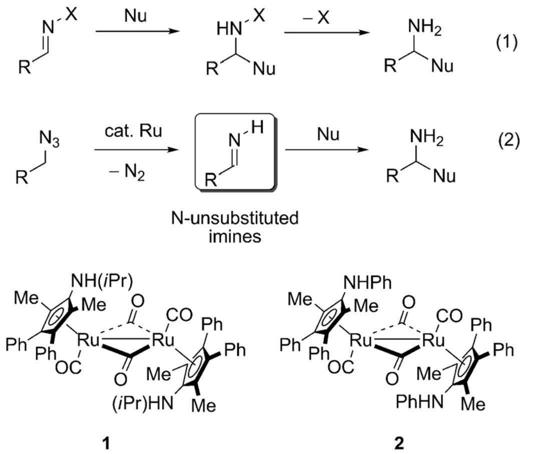

Figure 1. N-unsubstituted imines: Basic concept.

Unlike N-substituted imines, however, the synthetic scope of N-unsubstituted imines is still very limited. N-unsubstituted imines are known to be much less stable than the N-substituted analogues. This feature is easily addressed by the fact that only few N-unsubstituted imines have been successfully isolated or characterized.[3,4] In fact, such imines have been proposed as an intermediate without isolation (or detection) in most cases. For example, Chen and Brown,[5] and Itsuno et al.[6] suggested that N-unsubstituted imines could be formed from the N-trialkylsilyl imine precursors, but the scope of this method is restricted to the preparation of non-enolizable imines. In addition, N-unsubstituted imines are not generally obtained as a stable entity in the conventional reaction of carbonyl compounds with ammonia (only limited examples such as *ortho*-hydroxyarylketimines are known to be stable under these reaction conditions)[7]. Recently, Kobayashi and co-workers[8] and Thadani and co-workers[9] reported the aminoallylation of carbonyl compounds in one-pot, wherein the N-unsubstituted imines were not detected, but proposed as plausible intermediates. The use of excess ammonia in these cases poses a limitation in terms of the scope of the nucleophiles that react with N-unsubstituted imines. For example, the asymmetric allylation of N-unsubstituted imines using this method showed only poor enantioselectivity. In the meantime, N-metalloimines generated from alkyl cyanides have been frequently used as a surrogate for N-unsubstituted imines in C–C bond formation reactions and reductions.[10–13] However, this method requires highly reactive chemical reagents in stoichiometric amounts. As illustrated by these few examples, developing general synthetic methods for N-unsubstituted imines under mild reaction conditions represents a formidable challenge, and remains elusive in organic synthesis.

From a conceptual viewpoint, N-unsubstituted imines can be potentially accessed from easily available alkyl azide precursors with the removal of N_2 and subsequent migration of hydrogen [Eq. (2), Figure 1].[14] This method is particularly attractive because the reaction can proceed under very mild reaction conditions. In fact, stoichiometric formation of a metal/imine complex based upon this concept has already been reported.[15–18] However, attempts using photolytic[19] or metal-catalyzed conditions[20] could not deliver the free N-unsubstituted imines, presumably because of the instability and the high reactivity of the imines. Recently, we reported a simple synthesis of an isolable bridged diruthenium complex **1** and its utility under photolytic conditions for the racemization of secondary alcohols[21] and the chemoselective hydrosilylation of aldehydes.[22] Herein, we report that N-unsubstituted imines can be efficiently generated using **1** and the structurally related ruthenium complex **2**.[23,24] Remarkably, the mild reaction conditions used in this transformation even allowed the observation of *cis*/*trans* isomers of the N-unsubstituted imines by NMR spectra taken at room temperature. Moreover, this new protocol enables various chemoselective transformations of N-unsubstituted imines.

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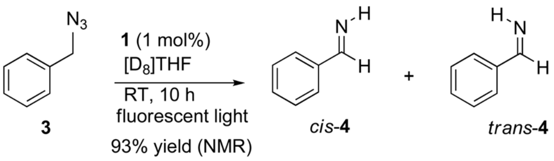
Our initial efforts focused on the synthesis of benzaldimine (**4**) from benzyl azide (**3**)under ruthenium-catalyzed photolytic conditions and unprecedented behavior of N-unsubstituted aldimines was observed [Eq. (3), Figure 2]. In the presence of 1 mol % of the catalyst **1** under a household fluorescent light (30 W) in [D$_8$]THF, the substrate was completely consumed after 10 hours at room temperature. Remarkably, a significant amount of benzaldimine (**4**; 93 % yield as determined by NMR analysis) was observed under these mild reaction conditions with no undesired events as previously reported in the literature (Figure 2).[25] In addition, the ^{1}H NMR spectrum of the crude reaction mixture showed two distinct sets (each with two doublets) of peaks for the imino hydrogen in approximately a 5:1 ratio. Based upon the coupling constant ($J = 16$ Hz), the major set of peaks was assigned to *cis*-**4** (Figure 2). The minor set has a significantly larger coupling constant ($J = 25$ Hz) and were therefore assigned to *trans*-**4**. Notably, **4** as prepared under these neutral conditions was quite stable. No significant decomposition was seen in the [D$_8$]THF solution, even after one day at room temperature. This observation is in sharp contrast to the previous reports which described only *cis*-**4** as a very unstable species.[3] Lowering the temperature somewhat increased the relative ratio of *cis*-**4**. On the basis of the relative integration of the peaks in the NMR spectrum of the crude reaction mixture, the ΔG value between two geometrical isomers in [D$_8$]THF was determined to be about 1 kcal mol^{-1}.[26] It should be also noted that both the ruthenium catalyst and fluorescent light were required for the imine formation. The catalytic reaction in the dark as well as the photolytic reaction without **1** showed no conversion.



(3)

T [°C]	*cis/trans*	ΔG *cis/trans* [kcal mol^{-1}]
25	5.08:1	0.97
-20	6.77:1	1.00
-60	8.65:1	0.92

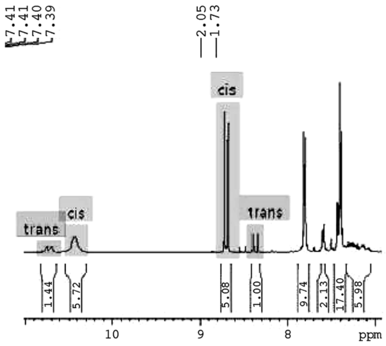
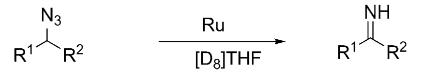
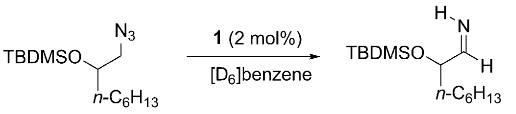


Figure 2. NMR spectrum of *cis*-**4** and *trans*-**4**. THF = tetrahydrofuran.

Encouraged by these results, we explored the synthesis and detection of other structurally diverse N-unsubstituted imines. As shown in Equation (4), the outcome depended upon the structure of the alkyl azide substrates. For example, the secondary benzylic azide **5** was completely converted into the ketimine **6** in greater than 90 % yield (NMR) in the presence of the ruthenium complex **2** (2 mol %). In this case, the ^{1}H NMR spectrum taken at room temperature showed the presence of the *cis/trans* isomers in a 2.9:1 ratio (for the spectral data and the assignment of *cis/trans* isomers, see the Supporting Information). In addition, bis(benzylic) azide (**7**) was completely consumed within 12 hours to give the chromatographically stable N-unsubstituted diphenylketimine **8** in 91 % yield upon isolation. Unlike the benzylic azides, the reaction of the aliphatic primary alkyl azide **9** was considerably slow. Also, the yield of the aldimine products **10** as measured by ^{1}H NMR spectroscopy was significantly lower [a small triplet/doublet peak at about $\delta = 8.00$ ppm ($J =$ 22 Hz, 4 Hz) is indicative of imine formation]. Interestingly, an aldimine possessing a silyl ether at the neighboring carbon atom (**12**) could be obtained from the azide precursor **11** in 82 % yield [Eq. (5)]. In this case, the NMR spectrum showed that the major species exists as the *trans* isomer. To additionally verify imine formation, we pursued in situ capture of the imine product with triethylborane under the photolytic conditions. As shown in Equation (6), generation of the borane imine adduct **13** was indeed observed by ^{1}H NMR spectroscopy (the characteristic doublet peak at $\delta = 9.41$ ppm was assigned to the imino hydrogen atom). This analysis is again in good agreement with previous reports on the characterization data obtained for the borane imine complex **13**,[5] and thus unambiguously confirms formation of N-



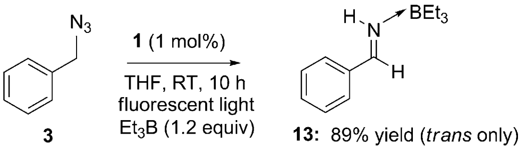
5: R^1 = Ph: R^2 = CH$_3$	**2** (2 mol%)	**6**: >90% yield (NMR) *cis/trans* = 2.9:1 at RT	(4)
7: R^1 = Ph: R^2 = Ph	**1** (1 mol%)	**8**: 91% yield (isolated)	
9: R^1 = *n*-C$_7$H$_{15}$; R^2 = H	**1** (2 mol%)	**10**: trace (~10%)	



(5)

11

12: 82% yield (NMR)
cis/trans = 1:3.1 at RT

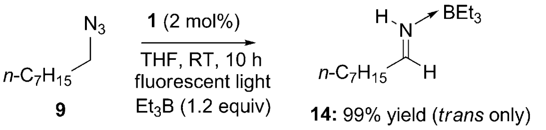


(6)

3

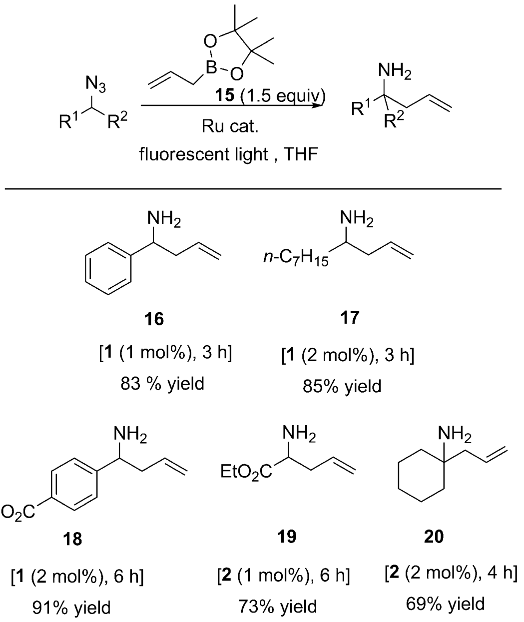
13: 89% yield (*trans* only)

unsubstituted imines from benzyl azide. Notably, even the borane complex of the aliphatic N-unsubstituted aldimine **14** could be obtained from **9** in high yield [Eq (7); the characteristic doublet peak at $\delta = 8.87$ ppm was assigned to the imino hydrogen atom).

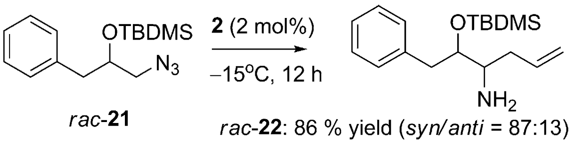


(7)

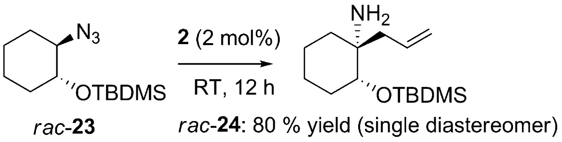
Having established the chemoselective access to various N-unsubstituted imines, we then explored the synthetic utility of these compounds. On the basis of the facile formation of the triethylborane adduct shown in Equations (6) and (7), the one-pot imine formation/allylation sequence was first explored using the commercially available **15** (1.5 equiv) as the allylating agent (Scheme 1). To our delight, the preliminary reaction of benzyl azide under the ruthenium-catalyzed photolytic conditions gave the aromatic allylic amine **16** in 83 % yield upon isolation when the catalyst **1** (1 mol %) was employed. In addition, the aliphatic homoallylic amine **17** was obtained in comparable yield (85 %). The unique chemoselectivity of the proposed reaction is highlighted by the formation of the amine **18**, which possesses an ester group, in 91 % yield. Notably, the scope of the reaction was successfully expanded to the synthesis of the allylated α-amino ester **19**, which could not be easily accessed by the previous studies which relied on the use of excess ammonia or strong reducing agents. In this case, the reaction with **1** was slow, but use of **2** (1 mol %) significantly improved the reactivity, thus producing **19** in 73 % yield. Synthesis of the tertiary carbinylamine **20** was also successful when **2** was employed. In addition to the simple allylation discussed above, the one-pot reaction of azides also showed excellent substrate-controlled diastereoselectivity. For example, the azide **21** gave the amine **22** in 86 % yield with 87:13 *syn* selectivity [Eq. (8); TBDMS = *tert*-butyldimethylsilyl]. In addition, the cyclohexyl azide **23** gave the allylated product **24** in 80 % yield as a single diastereomer [Eq (9)]. These examples demonstrate the potential synthetic utility of the reaction as the substrates are easily accessed from the corresponding epoxides[27] (for detailed procedures on the synthesis of the substrates, see the Supporting Information). As demonstrated by the efficient preparation of **25** and **26**, the reaction also showed an excellent level of reagent-controlled diastereoselectivity [Eqs. (10) and (11); Pin = pinacol].



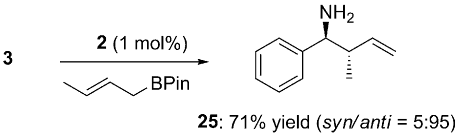
Scheme 1. Examples of the imine formation/allylation sequence.



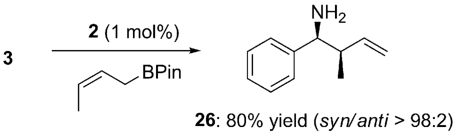
(8)



(9)



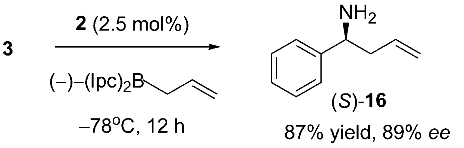
(10)



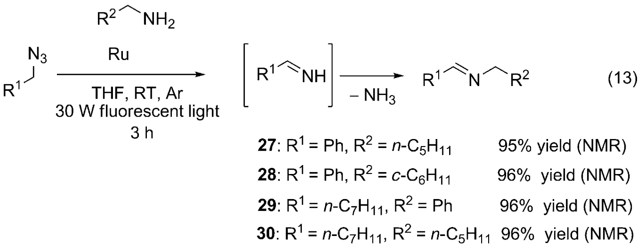
(11)

Finally, it should be emphasized that the mild reaction conditions enabled the asymmetric allylation of the in situ generated **4** using the chiral allylboronate species.[28,29] For example, employing the (−)-$(Ipc)_2B$ at −78 °C in the presence of 2.5 mol % of **2** gave the product (*S*)-**16** in 87 % yield with 89 % *ee* [Eq. (12); Ipc = isopinocampheyl].

We then explored the reaction of N-unsubstituted imines with heteroatom nucleophiles. As shown in Equation (13), we discovered that various N-unsubstituted imines generated from the azide precursors react with primary amines to give N-substituted imines in near-quantitative yields with no need for additives. Notably, enolizable N-unsubstituted aldimines proved efficient for this transformation, as indicated by the high yield for the synthesis of imines **29** and **30**. In addition,

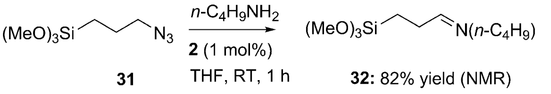


(12)



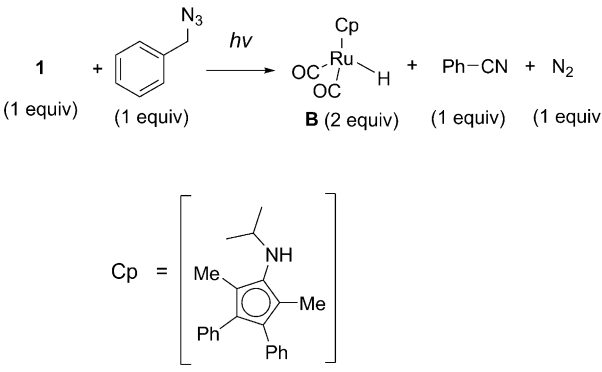
(13)

the water-sensitive trimethoxysilane **31** also gave the corresponding imine **32** in high yield [Eq. (14)].

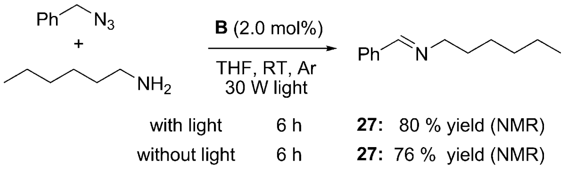


(14)

As discussed above, the chemoselective generation of the N-unsubstituted imine species seems to be the key event in the proposed reaction. Additional studies provided insights into the mechanism of formation of the N-unsubstituted imines. Treatment of the benzyl azide **3** with a stoichiometric amount of **1** generated the Ru-H species **B** and benzonitrile [Eq. (15)]. Moreover, the isolated Ru-H species **B** effectively catalyzed the formation of the N-substituted imine **27** from benzyl azide [Eq. (16)]. Notably, the fluorescent light was not necessary in this case. This result strongly suggests that the Ru-H species **B**[30] may be involved as a catalytically active species for the conversion of azides into N-unsubstituted imines. In addition, the use of fluorescent light is needed only for the generation of **B**.

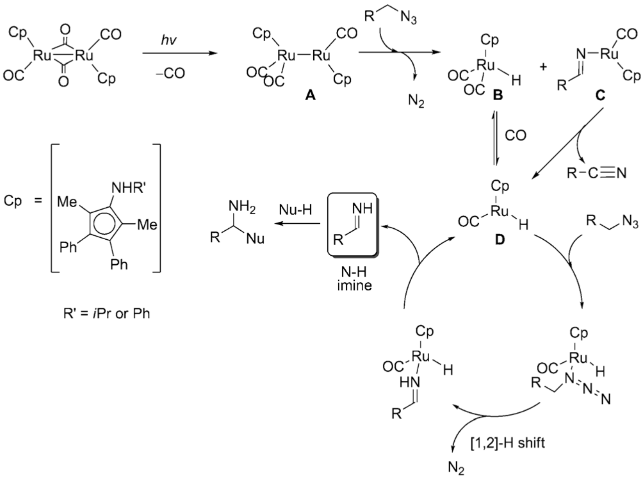


(15)



(16)

On the basis of this information, a plausible reaction sequence can be suggested (Scheme 2). The photogenerated ruthenium complex **A** attacks the azide to generate the Ru-H species **B** and the benzonitrile, presumably by way of the formation of the imido complex **C**. Upon losing a CO ligand,[31] **B** is converted into the coordinatively unsaturated species **D**. The high reactivity of this ruthenium complex facilitates the conversion of azides into imines. The resulting imine species might be weakly coordinating to the ruthenium center. The dissociation of the imine from the ruthenium complex could be promoted by the subsequent reaction with amine nucleophiles or allylboranes.



Scheme 2. Proposed mechanism for the imine formation.

In summary, we developed a novel ruthenium catalyst system which enabled generation of various N-unsubstituted imines under mild reaction conditions. As demonstrated by the observation of geometrical isomers of the enolizable N-unsubstituted imines, chemoselective preparation of structurally well-defined N-unsubstituted imines was of crucial importance. It is clear that the protocol introduced here opens up new possibilities in ideal amine synthesis. Expanding the synthetic scope of N-unsubstituted imines is now in progress.

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