Diastereoselective allylation and crotylation of *N*-unsubstituted imines derived from ketones†

Bhartesh Dhudshia, Jorge Tiburcio and Avinash N. Thadani*

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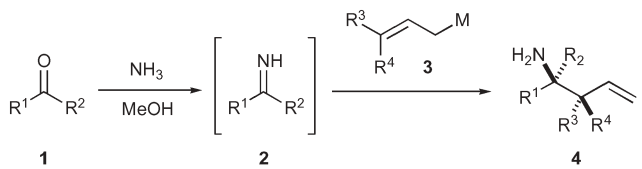
A wide variety of tertiary carbinamines are synthesized in high yields *via* diastereoselective allylation and crotylation of *in situ* generated *N*-unsubstituted ketimines.

Research into the addition of allyl organometallics to carbonyl compounds and their derivatives continues to proceed unabated—a consequence of the fact that the resulting homoallylic products have proven to be valuable synthons.[1] The majority of the research, however, has focused on the addition of these organometallics to aldehydes and, to a lesser extent, ketones.[2] Until recently, the expansion of the substrate scope to include imines and their derivatives had received limited attention.[3,4]

As part of an alkaloid synthesis program, we required a tertiary carbinamine (**4**) that we anticipated could be synthesized through crotylation of an *N*-unsubstituted ketimine (**2**)—a previously unknown reaction. Inspired by the elegant report of aminoallylation of aldehydes by Kobayashi and coworkers,[5] we sought to develop a robust methodology for the diastereoselective allylation and crotylation of **2** (Scheme 1).

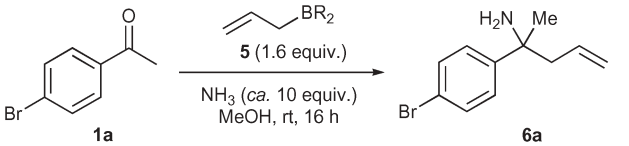
We surveyed a number of methods to synthesize and isolate the requisite substrate (**2**),[6] but concluded that a three-component reaction of the ketone, excess ammonia and the allylorganometallic (**3**) was the most efficient and effective protocol to generate the desired homoallylic amines. We suggest that *N*-unsubstituted ketimine (**2**) is formed *in situ* prior to its reaction with the allylorganometallic,[5,7–9] but our hypothesis needs further detailed validation. Next, we investigated the addition of a series of allyl organometallics to the *in situ* generated ketimine **2** (R^1 = 4-BrC_6H_4, R^2 = Me). The allylboron class of reagents were demonstrably superior in terms of reactivity and chemoselectivity.[10] A more detailed investigation of a range of allylboron compounds was undertaken in order to ascertain the reagent of choice (Table 1). As anticipated, the more reactive allylboron reagents, **5d** and **5e**,[11] displayed the highest efficacy in terms of isolated yields of homollylic amine **6a** (entries 4 and 5). A major issue of concern in all these reactions—chemoselectivity of imine *versus* ketone addition—was addressed by analyzing the organic extracts from the acid–base workup of **6a** (entries 4,5). It was determined that the corresponding homoallylic alcohol of **6a** was formed in minor amounts (⩽5%). We decided to continue our studies with allylboronic acid (**5e**) due to its ease of preparation and the simple purification of the resulting products.[12]

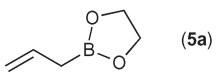
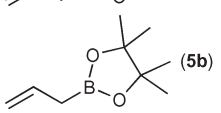
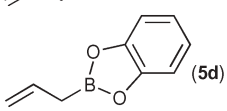
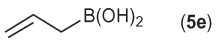


Scheme 1 Diastereoselective allylation and crotylation of *in situ* generated ketimines.

A series of ketones were then reacted with reagent **5e** in methanolic ammonia (Table 2).‡ Aliphatic (entries 1–4), electron rich aromatic (entry 5), electron deficient aromatic (entries 6 and 7), α,β-unsaturated (entry 8), cyclic (entries 9 and 10) and heterocyclic-substituted (entries 11 and 12) ketones were successfully allylated under the standard conditions. The resulting homoallylic amines (**6**) were easily isolated in high yields through simple acid–base extraction, and in all cases but one, did not require any further purification. A variety of functional groups are tolerated in the reaction sequence including the nitro (entry 7), cyano (entry 6),

Table 1 Addition of allyl boron reagents (**5**) to *N*-unsubstituted ketimine derived from **1a**



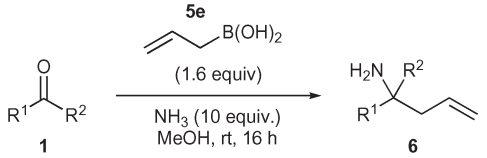
Entry	5	Yield of **6a** (%)[a]
1	 (**5a**)	35
2	 (**5b**)	29
3	 (**5c**)	43
4	 (**5d**)	70[b,c]
5	 (**5e**)	79[b]

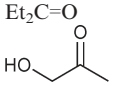
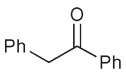
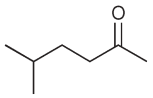
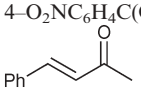
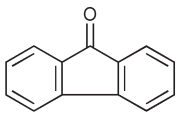
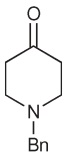
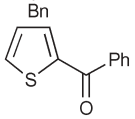
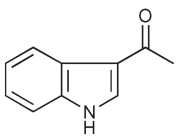
[a] Isolated yield after acid–base extraction. [b] Analysis (^{1}H NMR, 2,4,6-trimethylbenzene standard) of the organic phase from the acid–base work-up revealed ⩽5% of the corresponding homoallylic alcohol. [c] Isolated yield after acid–base extraction and preparative TLC.

Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada N9B 3P4. E-mail: athadani@uwindsor.ca; Fax: 1 519 973 7098; Tel: 1 519 253 3000 ext. 3556

† Electronic supplementary information (ESI) available: Experimental details and full characterization data (^{1}H, ^{13}C NMR, IR, HRMS) for all new compounds. See DOI: 10.1039/b511411j

Table 2 Reaction of *N*-unsubstituted imines derived from ketones with allylboronic acid (**5d**)[a]



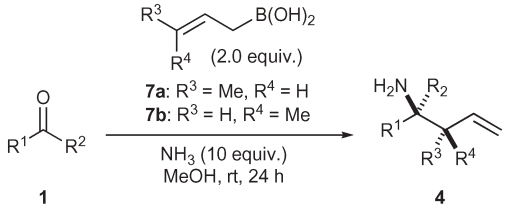
Entry	Ketone		Yield/%[b]
1	$Et_2C{=}O$	(**1b**)	73 (**6b**)
2		(**1c**)	80 (**6c**)
3		(**1d**)	78 (**6d**)
4		(**1e**)	85 (**6e**)
5	$4\text{–}MeOC_6H_4C(O)CH_2CH_3$	(**1f**)	72 (**6f**)
6	$4\text{–}NCC_6H_4C(O)CH_3$	(**1g**)	80 (**6g**)
7	$4\text{–}O_2NC_6H_4C(O)CH_3$	(**1h**)	87 (**6h**)
8		(**1i**)	70 (**6i**)[c]
9		(**1j**)	78 (**6j**)
10		(**1k**)	92 (**6k**)
11		(**1l**)	75 (**6l**)
12		(**1m**)	80 (**6m**)

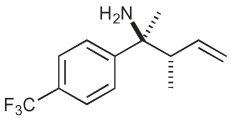
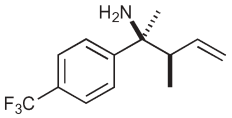
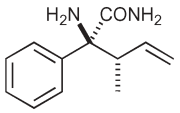
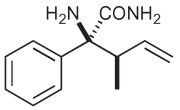
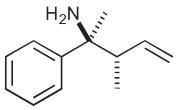
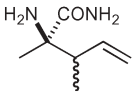
[a] Standard reaction conditions: A solution of the ketone (0.5 mmol), ammonia (*ca.* 7N in MeOH, 0.75 mL, *ca.* 10 equiv.) and allylboronic acid (**5e**) (2M in MeOH, 0.40 mL, 0.80 mmol) was stirred for 16 h at rt. [b] Isolated yield after acid–base extraction. [c] Isolated yield after acid–base extraction, and preparative TLC.

unprotected hydroxy (entry 2) and amino groups (entry 12). We were, however, unable to extend the substrate scope to include ketones that are either sterically hindered (*e.g.* pinacolone) or contain active methylene groups (*e.g.* ethyl acetoacetate) under the current conditions.

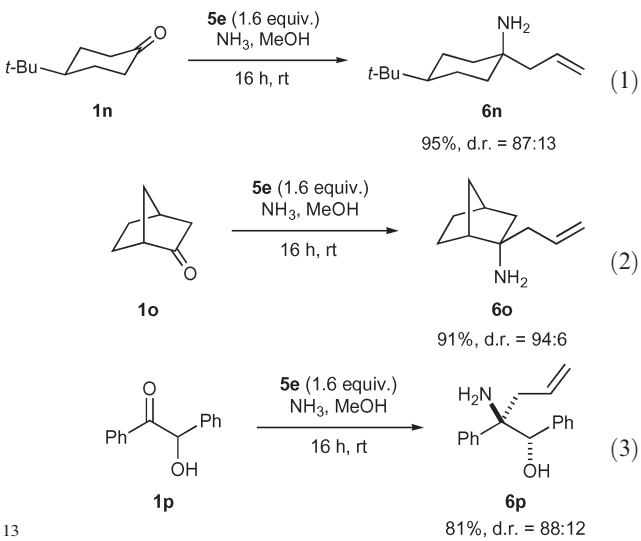
We next sought to investigate the allylation of ketones containing a pre-existing stereocenter. The substrates (**1n–q**) were subject to the standard set of reaction and work-up conditions, the results of which are shown in eqns (1)–(4). Good to excellent yields of tertiary carbinamines **6n–q** were obtained in all cases, while the observed diastereoselectivities, as determined by ^1H NMR, varied from modest for the reaction of 4-*tert*-butylcyclohexanone, norchamphor, and benzoin[13] (eqns (1), (2) and (3), respectively) to excellent for verbenone (eqn (4)).

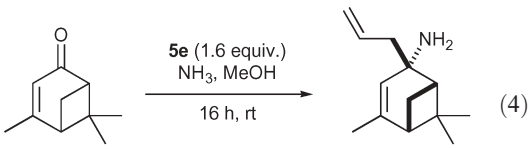
Table 3 Reaction of *N*-unsubstituted ketimines with (*E*)- and (*Z*)-crotylboronic acid (**7a/b**)[a]



Entry	Crotyl reagent	Product	Yield/%[b]	d.r.
1	**7a**		80 (**4a**)	97 : 3
2	**7b**		73 (**4b**)[c]	96 : 4
3	**7a**		95 (**4c**)[d]	97 : 3
4	**7b**		92 (**4d**)[d]	96 : 4
5	**7a**		50 (**4e**)	97 : 3
6	**7a**		88 (**4f**)[e]	60 : 40

[a] Standard reaction conditions: ketone (0.5 mmol), ammonia (*ca.* 7N in MeOH, 0.75 mL, *ca.* 10 equiv.) and crotylboronic acid (**7a/b**) (2M in MeOH, 0.50 mL, 1.00 mmol) were stirred for 24 h at rt. [b] Isolated yield after acid–base extraction. [c] Isolated yield after acid–base extraction, and preparative TLC. [d] Methyl benzoylformate was employed as the starting ketone, and aminolysis of the ester was observed. [e] Methylpyruvate was employed as the starting ketone, and aminolysis of the ester was observed.





1q 6q 84%, d.r. = 97:3 (4)

Finally, crotylation of a select number of ketones was examined under a slightly modified set of conditions (2.0 equiv. of **5e**, 10 equiv. of NH_3, rt, 24 h) (Table 3). Excellent diastereoselectivities were obtained with acetophenone derivatives (entries 1–5). The *anti* diastereomer (**4a/c**) was formed when (*E*)-crotylboronic acid (**7a**) was employed as the reagent, while (*Z*)-crotylboronic acid (**7b**) afforded the *syn* diastereomer (**4b/d**). The stereochemistry of the crotylated products **4** were assigned based upon the reaction of **7a** with acetophenone (entry 5) which afforded the previously known *anti* diastereomer **4e** in moderate yield and excellent diastereoselectivity (d.r. = 97:3).[4a] Crotylation of methylpyruvate (entry 6), on the other hand, was not diastereoselective likely due to the similar steric sizes of the methyl and methylformate groups. The results from entries 3, 4 and 6 also constitute a convenient route to α-allylated amino acid derivatives.[14]

In summary, an easily executable three component methodology for allylation of *N*-unsubstituted imines derived from a diverse range of ketones has been presented. The resulting homoallylic amines were isolated in good to excellent yields through simple acid–base extraction. More importantly, the crotylation of *N*-unsubstituted ketimines was also shown to be highly diastereoselective. We are currently striving to ameliorate the described methodology by expanding the substrate scope and developing enantioselective variants.

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References

‡ *General experimental procedure for allylation of N-unsubstituted ketimines*: To solution of the ketone (0.5 mmol) in ammonia (*ca.* 7N in MeOH, 0.75 mmol, *ca.* 10 equiv.), previously stirred for 15 min at rt, was added a freshly prepared solution of allylboronic acid (**5e**) (2M in MeOH, 0.4 mL, 0.80 mmol) dropwise over 5 min. The reaction mixture was subsequently stirred for 16 h at rt. The volatiles were removed *in vacuo* and the residue redissolved in Et_2O (15 mL). Aqueous HCl (1N, 15 mL) was next added dropwise. The biphasic mixture was vigorously shaken, and the layers separated. The acidic aqueous layer was washed with Et_2O (3 × 15 mL), and made basic by the addition of solid NaOH (*ca.* 5 g). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($NaSO_4$), filtered and concentrated *in vacuo* to afford the desired tertiary carbamine **6**.

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3 For selected recent examples of addition of allylorganometallics to aldimine derivatives, see: (*a*) C. Bellucci, P. G. Cozzi and A. Umani-Ronchi, *Tetrahedron Lett.*, 1995, **36**, 7289; (*b*) H. Nakamura, K. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 4242; (*c*) F. Fang, M. Johannsen, S. Yao, N. Gathergood, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1999, **64**, 4844; (*d*) T. Gastner, H. Ishitani, R. Akiyama and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2001, **40**, 1896; (*e*) H. C. Aspinall, J. S. Bissett, N. Greeves and D. Levin, *Tetrahedron Lett.*, 2002, **43**, 323; (*f*) M. Sugiura, F. Robvieux and S. Kobayashi, *Synlett.*, 2003, 1749; (*g*) R. A. Fernandes and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 735; (*h*) S.-W. Li and R. A. Batey, *Chem. Commun.*, 2004, 1382; (*i*) I. Shibata, K. Nose, K. Sakamoto, M. Yasuda and A. Baba, *J. Org. Chem.*, 2004, **69**, 2185; (*j*) C. Ogawa, M. Sugiura and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6491.

4 For selected recent examples of addition of allylorganometallics to ketimine derivatives, see: (*a*) C. Ogawa, M. Sugiura and S. Kobayashi, *J. Org. Chem.*, 2002, **67**, 5359; (*b*) S. Yamasaki, K. Fujii, R. Wada, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2002, **124**, 6536; (*c*) R. Berger, K. Duff and J. L. Leighton, *J. Am. Chem. Soc.*, 2004, **126**, 5686; (*d*) H. Ding and G. K. Friestad, *Synthesis*, 2004, 2216.

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8 For example, when ketone **1n** is dissolved in ammonia-saturated CD_3OD, the ^{13}C NMR signal changes from δ 215.37 (the ketone chemical shift) to δ 187.25 (what we presume to be the chemical shift of the *N*-unsubstituted imine **2**). We are currently examining the mechanism of the three-component reaction in greater detail.

9 It has been previously established through theoretical studies that compound **2** (R^1 = Ph, R^2 = Me) preferentially exists in the ketimine form as opposed to the enamine tautomer: G. Erker, M. Riedel, S. Koch, T. Jödicke and E.-U. Würthwein, *J. Org. Chem.*, 1995, **60**, 5284.

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11 H. C. Brown, U. S. Racherla and P. J. Pellechia, *J. Org. Chem.*, 1990, **55**, 1868.

12 Pending further mechanistic studies, the possibility remains that the active allylating species is *in situ* generated *B*-allyldimethoxyborane and/or *B*-allyldiaminoborane.

13 The structure of **6p** was confirmed by X-ray crystallography. *Crystal data,* **6p**: $C_{17}H_{19}NO$, M = 253.33, monoclinic, space group $P2_1/n$, a = 12.143(2) Å, b = 6.261(1) Å, c = 18.975(4) Å, β = 97.148(2)°, V = 1431.4(5) Å^3, Z = 4, T = 173(2) K, μ(Mo Kα) = 0.073 mm^{-1}, 2519 independent reflections (R_{int} = 0.0424), $R1$ = 0.0433, $wR1$ = 0.0931, (1853 reflections, $I > 2\sigma I$), $R2$ = 0.0661, $wR2$ = 0.1031, (all data). Goodness-of-fit ($F2$) = 1.011. Data were collected on a Bruker APEX CCD instrument and solutions performed using the SHELXTL 5.03 Program Library, Siemens Analytical Instrument Division, Madison, WI, USA, 1997. CCDC 283664. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511411j.

14 Aminolysis of the ester functionality present in the starting ketones [methyl benzoylformate (Table 3, entries 3,4); methylpyruvate (Table 3, entry 6)] was observed in the final products (**4c–4e** respectively).