# Diastereoselective Addition of Nucleophiles to the C3 Position of *N*-(Tosyloxy)-β-lactams

**Min Teng and Marvin J. Miller***

*Contribution from the Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556.* *Received August 21, 1992*

**Abstract:** *trans*-3-Substituted-β-lactams **22a-j** are conveniently synthesized by treating **21** with suitable nucleophiles in the presence of $Et_3N$ or $(i\text{-}Pr)_2EtN$. The key aspects of this method relative to traditional methods are that the C3 position of β-lactam **21** acts as an *electrophilic* center and the addition of nucleophiles is accompanied by N–O bond cleavage. The reaction is tolerant of a variety of alkyl groups at the C4 position, although an electron-withdrawing group at C4 is detrimental. The rate of reaction is increased if an electron-withdrawing group is present at the C3 position. Base-initiated enolization followed by an $S_N2'$ displacement of tosylate by a nucleophile is mechanistically consistent with these observations, but enolization is considered to be the rate-determining step. Suitable sources of nucleophiles are TMSX, $Et_3NH\cdot X$, or $(i\text{-}Pr)_2EtNH\cdot X$, while $Bu_4N\cdot X$ or LiX initiates the formation of a byproduct, **31**. Triethylamine has been found to act as a competitive nucleophile to form **30** and therefore was not the preferred base for the reaction. The yield of product can be optimized by using a non-nucleophilic base, such as $(i\text{-}Pr)_2EtN$, and an excess of nucleophile.

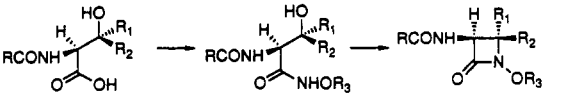
## Introduction

The discovery[1] and subsequent studies[2] of monobactams and other monocyclic β-lactams[3] have significantly expanded structure–activity relationship (SAR) studies of β-lactam antibiotics, which continue to be the most widely used class of antimicrobial agents. Besides the developing interest in their intrinsic antibacterial activity, monocyclic β-lactams frequently serve as precursors for the synthesis of bicyclic β-lactam antibiotics. In fact, derivatizing monocyclic β-lactams often provides both unique β-lactam antibiotics and chemical challenges.

A number of methods are now available for the synthesis of monocyclic β-lactams. Our early studies in this field led to the development of a two-step hydroxamate-mediated synthesis of β-lactams **3** from the corresponding β-hydroxy acids **1** (Scheme I).[4] The key step in this process is the biomimetic formation of the N–C4 bond with inversion of stereochemistry at C4. While a number of non-hydroxamate-based N–C4 cyclizations have been reported[5] and are effective for the synthesis of specific antibiotics,[6] *N*-hydroxy-β-lactams **4** have proven to be notably versatile synthetic intermediates (Scheme II).[7] In this paper we report the details of another remarkable reaction of forms of this intermediate: the direct addition of nucleophiles to the C3 position of *N*-(tosyloxy)-β-lactams (**4** → **5**). While our studies on this novel reaction are still qualitative, the physical organic studies for the support of the proposed mechanisms are being conducted and will be published elsewhere.

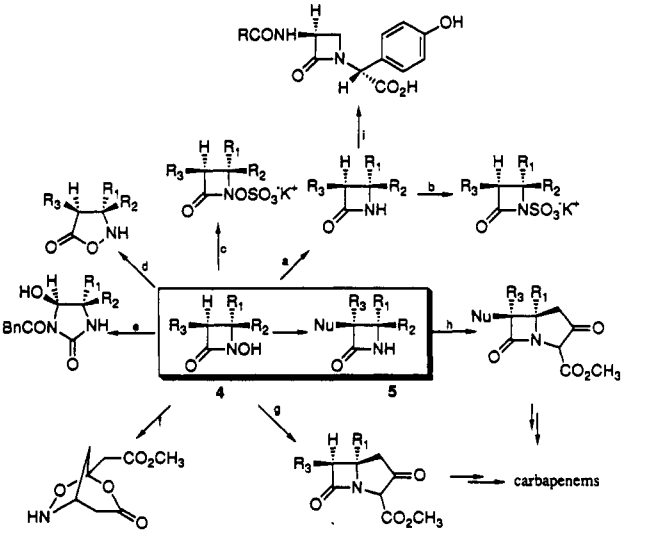
Typically, addition of electrophiles to the C3 position of β-lactams (Scheme III) requires the formation of an enolate **7**, which

**Scheme I**




1 2 3

**Scheme II**

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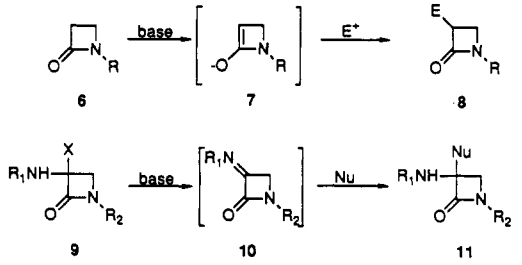
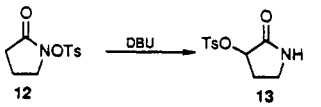
**Scheme III**

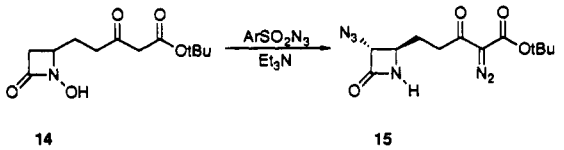


in turn reacts with an electrophile (**6** → **8**).[8] Nucleophilic addition to the C3 position of β-lactams (**9** → **11**), however, is not so straightforward. It can be performed only when the C3 position already contains two heteroatom substituents.[9] This limitation dictates that no 3-monosubstituted-β-lactam can be directly synthesized in this manner.

Our first indication of direct addition of a *nucleophile* to the C3 position of a cyclic hydroxamate was the observation that treatment of *N*-(tosyloxy)pyrolidinone (**12**) with DBU (eq 1)



(1)



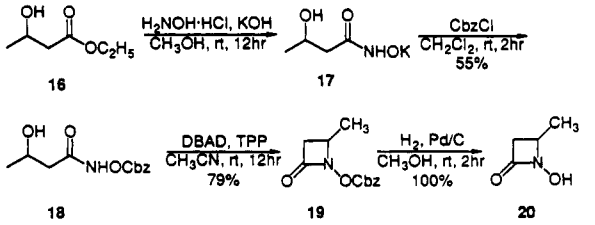
(2)

resulted in the formation of 3-(tosyloxy)-2-pyrolidinone (**13**).[10,11] Subsequently, we observed that treatment of *N*-hydroxy-β-lactam **14** with an excess of arylsulfonyl azide and triethylamine induced not only the expected diazo transfer but also concomitant N–O cleavage and the transfer of azide ion to the C3 position to give **15** (eq 2).[12] Now, it is fairly clear that the diazo transfer is mechanistically independent of the azide transfer and N–O bond cleavage. The latter two processes, however, are related. While the diazo-transfer reaction is well-known and has many synthetic applications,[13] it was the azide transfer and N–O bond cleavage that attracted our attention. The tremendous potential of this discovery prompted a more detailed study of this reaction.

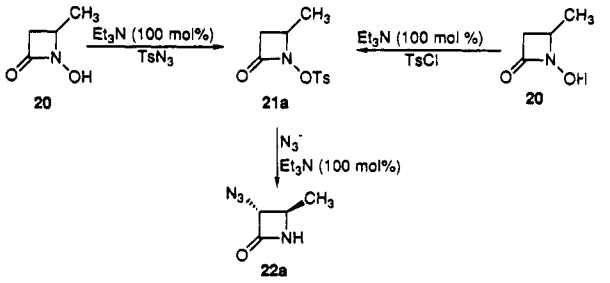
## Results and Discussion

To elucidate the scope and utility of the azide transfer and N–O bond cleavage reaction, an investigation was carried out on simple *N*-hydroxy-β-lactam **20**, which did not contain a β-keto ester side chain for competitive or simultaneous diazo-transfer reaction. β-Lactam **20** was conveniently prepared from the appropriate β-hydroxybutrate **16** (Scheme IV). Conversion of **16** to the hydroxamate salt **17** followed by a reaction with CbzCl afforded **18** in moderate yield. Mitsunobu reaction[14] of **18** under normal

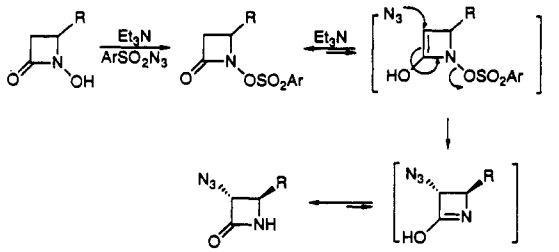
**Scheme IV**



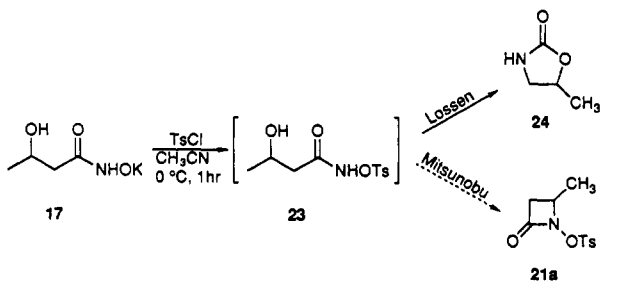
**Scheme V**



**Scheme VI**



**Scheme VII**



conditions provided β-lactam **19**. Finally, the Cbz group was removed by catalytic hydrogenolysis of **19** to afford **20** quantitatively.

Subsequent studies on **20** revealed that 1 equiv of tosyl azide and 2 equiv of triethylamine were optimal for the azide-transfer and N–O bond cleavage reaction. An insufficient amount of triethylamine led to incomplete reaction and therefore the isolation of an intermediate **21a**. The structure of **21a** was confirmed by an independent synthesis (Scheme V). This discovery indicated that tosylation of the *N*-hydroxy group was an essential prerequisite for the reaction.

Since the isolation of intermediate **21a**, a number of mechanisms rationalizing the simultaneous azide transfer and N–O bond cleavage were proposed. A generalized mechanism consistent with anti-addition of azide ion relative to the C4 substituent[15] is described in Scheme VI. A key aspect of this mechanism is thought

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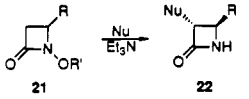
(15) Predominant anti addition of nucleophiles relative to the C4 substituent was invariably observed in our studies. The trans products were obtained exclusively with substrates possessing larger alkyl group than methyl at the C4 position (see Table I). For a related discussion, see: Gordon, E. M.; Sydes, R. B. *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; pp 199–370.

**Table I.** Reactions of **21a–c** with Nucleophiles (1.0–1.3 equiv) in the Presence of Triethylamine




**21** **22**

**21a**: R = $CH_3$, R' = Ts
**21b**: R = $CH_3$, R' = $PO(OPh)_2$
**21c**: R = $(CH_2)_2CO_2(CH_2)_2TMS$, R' = Ts

| entry | substrate | product | Nu | reagent | time, h | yield, % | anti/syn[a] |
|---|---|---|---|---|---|---|---|
| 1 | **21b** | **22a** | $N_3$ | $Et_3NH{\cdot}N_3$[b] | 36 | 56 | 24:1 |
| 2 | **21a** | **22b** | I | TMSI | 21 | 51 | 11:1 |
| 3 | **21a** | **22c** | Br | TMSBr | 48 | 44 | 9:1 |
| 4 | **21a** | **22d** | Cl | $Et_3NH{\cdot}Cl$[c] | 48 | 35 | 8:1 |
| 5 | **21a** | **22e** | OAc | $Et_3NH{\cdot}OAc$[c] | 96 | 34 | 7:1 |
| 6 | **21a** | **22f** | SPh | $Et_3NH{\cdot}SPh$[b] | 22 | 25 | 9:1 |
| 7 | **21c** | **22g** | $N_3$ | $TMSN_3$ | 19 | 62 | >20:1 |
| 8 | **21c** | **22h** | I | $Bu_4N{\cdot}I$ | 12 | 54 | >20:1 |
| 9 | **21c** | **22i** | SPh | $Et_3NH{\cdot}SPh$[b] | 24 | 38 | >20:1 |
| 10 | **21c** | **22j** | Cl | TMSCl | 22 | 50 | >20:1 |

[a] The ratio of anti/syn was determined from $^1H$ NMR spectrum of crude product. [b] These triethylammonium salts were generated in situ. [c] Triethylammonium chloride was prepared according to known procedure.[21]

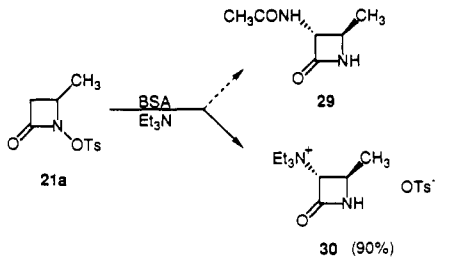
to be base-initiated enolization followed by an $S_N2'$ displacement of tosylate by azide ion.[16] However, rate-determining enolization followed by ionization and subsequent nucleophilic attack, as suggested by Hoffman's recent elegant studies on acyclic hydroxamates,[11c] has not been ruled out. Favorskii-type reactions of $\alpha$-haloamides reportedly give $\alpha$-lactams which can react with nucleophiles at either the $\alpha$-carbon or the acyl group.[17] A related process in the $\beta$-lactam substrates described here would require intermediacy of a highly strained bicyclo [1.1.0] system.[18]

Triethylamine-promoted enolization of $\beta$-lactam **21** is plausible since the presence of an electron-withdrawing tosyloxy group on the nitrogen would facilitate such a process. Consistent with this were our subsequent observations that *N*-(phosphoryloxy)-$\beta$-lactam **21b**[19] (entry 1, Table I) underwent the same reaction as **21a** upon treatment with azide ion in the presence of triethylamine, while $\beta$-lactams with poorer electron-withdrawing groups attached to the nitrogen, such as *O*-benzyl-, *O*-Cbz-, or *O*-acetyl-*N*-hydroxy-$\beta$-lactams, were ineffective. Parenthetically, the synthesis of **21a** by direct tosylation of hydroxamate **17** and planned cyclization did not give **23**. Instead, product **24**, derived from Lossen rearrangement[20] on **23**, was isolated in quantitative yield (Scheme VII).

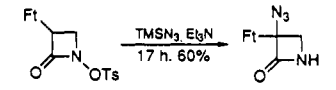
The successful transfer of azide ion to the C3 position of $\beta$-lactams prompted us to further explore transfer of other potentially useful functional groups. In fact, during the studies of the azide-transfer reaction, we had already encountered a competitive chloride-transfer and N–O bond cleavage reaction. Careful examination of the crude product from the reaction wherein **21a** was prepared by treating **20** and TsCl with triethylamine (Scheme V) revealed the formation of a small amount of *trans*-3-chloro-4-methyl-$\beta$-lactam (**22d**). Further study of this reaction indicated that the chloride-transfer and N–O bond cleavage process could be enhanced by using 2 equiv of triethylamine. Apparently, chloride ion from the in-situ generated $Et_3NH{\cdot}Cl$ was transferred to the C3 position of **21a** according to the same mechanism as the azide-transfer reaction.

Subsequent studies using different substrates and nucleophiles indicated that the reaction is quite general (Table I).[21] Interestingly, although bromide is a significantly better nucleophile than chloride, change of the nucleophile from chloride to bromide did not accelerate the reaction or improve the yield (entries 3 and 4) proportionally. This suggested that enolization is the rate-determining step. The yield of product increased slightly with increased nucleophilicity of the nucleophile (entries 2–5). Higher yields and greater diastereoselectivity were obtained when **21c**, with a larger substituent at C4, was used. The increased diastereoselectivity in reactions of **21c** is consistent with steric considerations. Since the C4 substituent is much larger in **21c** than in **21a**, the incoming nucleophile has a greater tendency to approach from the back side of the proposed enol relative to the C4 substituent of **21c**.

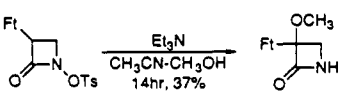
**Scheme VIII**




In contrast to traditional methods,[9] our method, being fairly general, not only allows for the preparation of 3-monosubstituted-$\beta$-lactams but 3-bisubstituted-$\beta$-lactams as well. Thus, treatment of 3-phthalimido-*N*-(tosyloxy)-$\beta$-lactam (**25**), derived from *N*-phthalimidoserine,[22] with $TMSN_3$ in the presence of $Et_3N$ provided 3-azido-3-phthalimido-$\beta$-lactam (**26**) smoothly (eq 3). Similarly, treatment of **25** with methanol in the presence of $Et_3N$ provided **27** (eq 4). Not surprisingly, the same reaction




**25** **26** (3)




**25** **27** (4)

(16) $S_N2'$ reactions on hydroxamates and related systems with leaving groups on nitrogen have been postulated previously. (a) For an $S_N2'$ reaction on acyloxypteridines, see: Taylor, E. C.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 4455. (b) For an $S_N2'$ reaction on *N*-chloroamines see: Hermkens, P. H. H.; Plate, R.; Kruse, C. G.; Sheeren, H. W.; Ottenheijm, H. C. J. *J. Org. Chem.* **1992**, *57*, 3881, footnote 37.

(17) Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25.

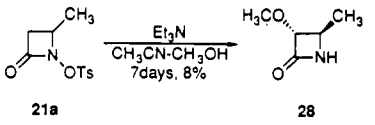
(18) Deyrup, J. A.; Clough, S. C. *J. Org. Chem.* **1974**, *39*, 902.

(19) The *O*-phosphoryl-*N*-hydroxy-4-methyl-$\beta$-lactam was prepared by treating **20** with phosphoryl azide in the presence of triethylamine. For the preparation and use of phosphoryl azide, see: Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

(20) (a) Bauer, L.; Exner, O. *Angew Chem., Int. Ed. Engl.* **1974**, *13*, 376. (b) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209.

(21) Triethylammonium chloride, diisopropylethylammonium chloride, and diisopropylethylammonium acetate were prepared according to the procedure used for triethylammonium azide. Saito, A.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *33*, 209.

(22) Nefkins, G. H. L.; Tesser, G. I.; Nivard, P. J. F. *Recl. Trav. Chim. Pays–Bas* **1960**, *79*, 688.



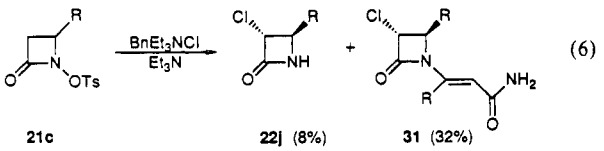

21a 28 (5)

(eq 5) for **21a** proceeded much slower and the product **28** was isolated in much lower yield. As expected, the phthalimido group at the C3 position of **25** increases the acidity of the C3 proton, and as a consequence, the enolization step is significantly facilitated. This result is again consistent with the suggestion that enolization is the rate-determining step.

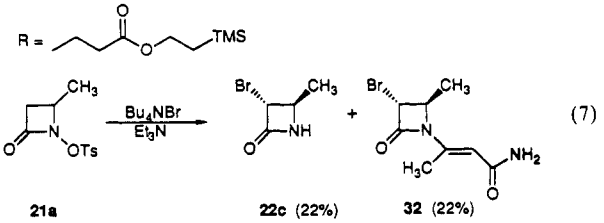
Optimization of the reaction conditions has been explored. It is advantageous to use an excess of nucleophile (>100 mol %) in the reaction. Use of 150 mol % instead of 100 mol % of nucleophile improved the yield of the product by about 10%.

Triethylamine has been found to function as a competitive nucleophile in one reaction wherein attempts were made to prepare 3-acetamido-β-lactam **29** by treating **21a** with bis(trimethylsilyl)acetamide[23] in the presence of triethylamine. To our surprise, 3-triethylammonium tosylate **30** was isolated in 90% yield and no **29** could be detected (Scheme VIII). On the basis of the above experiment and results in Table I (entries 2–5), competitive nucleophilic reaction of triethylamine, even when only 100 mol % was used, was thought to account for the relatively low yields of the desired nucleophilic substitution products **22**. Therefore, simultaneous use of a less nucleophilic base and excess nucleophile was studied. Indeed, as shown in Table II, reactions under these new conditions proceeded in much higher yield (compare entries 1–3 of Table II with entries 4–6 of Table I).

The effects of different counterions for a given nucleophile on the reaction also have been investigated. For instance, in the chloride-transfer reaction, change of reagent from $Et_3NH$·Cl to TMSCl did not affect the yield or the rate of the reaction significantly. However, an additional product (**31**) was produced when $BnEt_3NCl$ was employed as the potential source of chloride (eq 6). Compound **31** was observed to the exclusion of **22j** when LiCl was employed. Similarly, when TMSBr was replaced with $Bu_4NBr$ as the source of bromide, **32** was obtained along with the desired product **22c** (eq 7).




(6)




(7)

A plausible mechanism for the formation of **31** and **32** (Scheme IX) invokes the basic nature of quaternary ammonium or lithium salts. Variable amounts of quaternary ammonium hydroxide or lithium hydroxide are difficult to avoid in the corresponding halide salts due to the hygroscopic property of the latter. Being a strong base, the quaternary ammonium hydroxide or lithium hydroxide can initiate the elimination of a molecule of toluenesulfonic acid from **21c** to form imine **33**.[24] Nucleophilic attack of imine **33** by **22j** would provide bis(β-lactam) **34**, which might undergo

(23) Bis(trimethylsilyl)formamide has been reported to be a mild nucleophile. (a) Guest, A. W.; Harrington, F. P.; Milner, P. H.; Ponsford, R. J.; Smale, T. C.; Stachulski, A. V. *J. Chem. Soc., Chem. Commun.* **1984**, 1335. (b) Kaura, A. C.; Pearson, M. J. *Tetrahedron Lett.* **1985**, *26*, 2597.

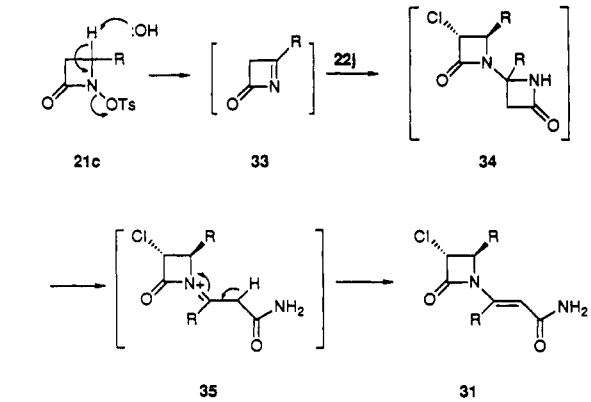
(24) Generation of related imines from 4-halo- or 4-acetoxy-β-lactams, followed by trapping with nucleophiles, has considerable precedent. (a) Gavina, F.; Costero, A. M.; Andreu, M. R. *J. Org. Chem.* **1990**, *55*, 435. (b) Clauss, K.; Grim, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, *539*, and references cited therein.

**Table II.** Reactions with Alternate Base and Excess Nucleophile

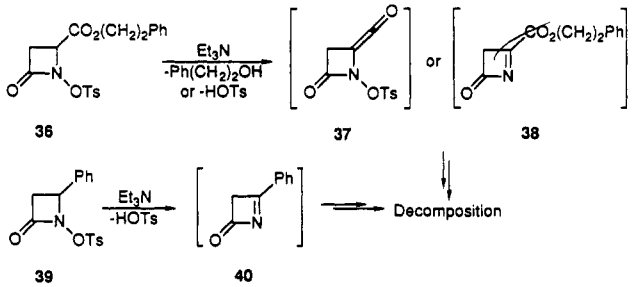
| entry | product | reagent | mol % | time, h | yield |
|---|---|---|---|---|---|
| 1 | **22d** | $(i\text{-Pr})_2$EtNH·Cl | 5.0 | 72 | 49 |
| 2 | **22e** | $(i\text{-Pr})_2$EtNH·OAc | 4.5 | 72 | 68 |
| 3 | **22f** | $(i\text{-Pr})_2$EtNH·SPh[a] | 1.5 | 24 | 38 |

[a] Salt was generated in situ.

**Scheme IX**




**Scheme X**




subsequent ring opening to form **35**. Finally, deprotonation of **35** would afford **31** (Scheme IX).

Detrimental removal of the C4 proton by base apparently becomes highly competitive with the C3 enolization process if R in **21** is an electron-withdrawing group. For instance, treatment of 4-[(phenylethyl)carboxy]-*N*-(tosyloxy)-2-azetidinone (**36**) in acetonitrile with $TMSN_3$ in the presence of $Et_3N$ at 0 °C immediately produced an intensive orange reaction mixture. Workup allowed isolation of only 2-phenethanol (54%). Similarly, when 4-phenyl-*N*-(tosyloxy)-2-azetidinone (**39**) was treated with $Et_3NH$·OAc in the presence of $Et_3N$, a brown solution resulted and no organic soluble products were obtained after workup (Scheme X).

While the decomposition mechanisms are yet undetermined, the acidification of the C4 proton by the pendant carboxyl group of **36** might promote initial elimination to either **37** along with phenethanol or **38** along with toluenesulfonic acid. Similarly, the phenyl group at the C4 position of **39** might facilitate the elimination of toluenesulfonic acid from **39** to form acylimine **40**, which was further decomposed into unisolable products. Experiments designed to trap and perhaps synthetically utilize proposed intermediates **38** and **40** are being considered.

In summary, we have demonstrated diastereoselective addition of a variety of nucleophiles to the C3 position of *N*-(tosyloxy)-β-lactams. The reaction is novel in that the C3 carbon behaves as an *electrophilic* center. Although electron-withdrawing groups, like $CO_2R$ or Ph, at C4 are detrimental, the reaction tolerates a variety of alkyl groups at the C4 position. On the other hand, an electron-withdrawing group at the C3 position was observed to facilitate the reaction significantly. To reduce side reactions, TMSX, $Et_3NH$·X, or $(i\text{-Pr})_2$EtNH·X was used as a suitable source of nucleophile. $(i\text{-Pr})_2$EtN was the preferred base over $Et_3N$ by virtue of its decreased nucleophilicity. The yield of product can be significantly improved when $(i\text{-Pr})_2$EtN and an excess of nucleophile are employed.

Diastereoselective addition of nucleophiles to the C3 position of β-lactams has considerable potential for simplification of the design and synthesis of a number of natural and unnatural β-lactams.[25] Applications to the syntheses of biologically interesting monocyclic and bicyclic β-lactams and other heterocycles are being investigated.

## Experimental Section

**General Methods.** Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were obtained on a General Electric GN-300 spectrometer and were performed in chloroform-*d*. $^1$H NMR chemical shifts are reported in parts per million relative to tetramethylsilane. *J* values are given in hertz. For $^{13}$C NMR, reference was the center peak of chloroform-*d* (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. TF refers to thin film, and KBr refers to potassium bromide disk. Electron impact mass spectra, chemical ionization mass spectra, and fast atom bombardment were recorded on an AEI Scientific Apparatus MS 902 and Finnigan MAT Model 8430 spectrometers. Analytical TLC was carried out using commercially available aluminum-backed 0.2-mm silica gel 60 F-254 plates. Flash silica gel column chromatography was conducted using Merck silica gel 60 (230–400 mesh). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

All reactions were periodically monitored by TLC and worked up after the complete consumption of starting materials unless specified otherwise. Solvents for flash column chromatography were distilled. Anhydrous methylene chloride, acetonitrile, and triethylamine were freshly distilled from $CaH_2$ and stored under nitrogen. All purchased reagents were of reagent grade quality and were used without further purification.

***O*-Cbz-3-hydroxybutyrohydroxamic Acid (18).** Hydroxylamine hydrochloride (572 mg, 8.20 mmol) and potassium hydroxide (462 mg, 8.25 mmol) were dissolved in absolute methanol (30 mL) in an ice bath. The solution was stirred for 30 min. The precipitates were removed by filtration through Celite. To this clear solution was added a solution of ethyl 3-hydroxybutyrate (Aldrich, 1.034 g, 7.85 mmol) and potassium hydroxide (462 mg, 8.25 mmol) in absolute methanol (20 mL). The reaction mixture was left for 12 h at room temperature and then was concentrated to afford a white solid. The white solid was washed with cold ethyl acetate–hexanes (1:3) and dried under vacuum. To the dried solid were added $CH_2Cl_2$ (20 mL) and CbzCl (1.34 mL, 9.40 mmol). The suspended mixture was vigorously stirred at room temperature for 2 h when the solution showed negative result to $FeCl_3$ test. The reaction mixture was filtered, and the clear solution was concentrated to provide **18** as a white solid (1.098 g, 55.4%, from ethyl acetate): mp 85.5–87 °C; $^1$H NMR δ 1.25–1.28 (d, *J* = 6.24, 3 H), 2.30–2.38 (dd, $J_1$ = 14.99, $J_2$ = 8.48, 1 H), 2.42–2.48 (dd, $J_1$ = 14.98, $J_2$ = 3.05, 1 H), 3.04 (b, 1 H), 4.20–4.25 (m, 1 H), 5.26 (s, 2 H), 7.37 (s, 5 H), 9.57 (b, 1 H); $^{13}$C NMR δ 22.86, 41.99, 64.73, 71.67, 128.52, 128.70, 129.00, 133.94, 154.70, 170.25; IR (KBr) 3370, 3140, 2980, 1800, 1680, 1530, 1460, 1385, 1240, 970 cm$^{-1}$; MS (CI) 254 ($M^+$H), 147, 107, 102, 91. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.74; H, 5.73; N, 5.58.

***O*-Cbz-*N*-hydroxy-4-methyl-2-azetidinone (19).** To a solution of **18** (625 mg, 2.47 mmol) and triphenylphosphine (713 mg, 2.72 mmol) in acetonitrile (10 mL) was added di-*tert*-butyl azodicarboxylate (DBAD, 625 mg, 2.72 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated, and the product was purified by column chromatography with ethyl acetate–hexanes (1:5) to afford **19** (460 mg, 79%) as a colorless oil: $^1$H NMR δ 1.41–1.43 (d, *J* = 6.11, 3 H), 2.46–2.51 (dd, $J_1$ = 13.79, $J_2$ = 2.66, 1 H), 2.99–3.06 (dd, $J_1$ = 13.78, $J_2$ = 5.52, 1 H), 4.13–4.18 (m, 1 H), 5.25, (s, 2 H), 7.39 (s, 5 H); $^{13}$C NMR δ 17.74, 39.75, 54.86, 71.67, 128.57, 128.68, 129.02, 133.73, 153.49, 163.78; IR (TF) 2980, 1805, 1775, 1230 cm$^{-1}$; MS 129, 91 (base peak), 77, 65. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.11; H, 5.65; N, 5.82.

***N*-(Tosyloxy)-4-methyl-2-azetidinone (21a).** *N*-Hydroxy-4-methyl-2-azetidinone (**20**) was obtained by catalytic hydrogenolysis of **19** (420 mg, 1.79 mmol) in methanol (10 mL) in the presence of 5% Pd/C (5.0 mg, 10% w/w) for 2 h. After filtration through Celite, the reaction mixture was concentrated under reduced pressure to provide **20** as a white solid. Because of the instability of *N*-hydroxy-β-lactams,[7d] compound **20** was used directly without further purification. To a solution of **20** and toluenesulfonyl chloride (358 mg, 1.88 mmol) in acetonitrile (10 mL) was added triethylamine (0.26 mL, 1.88 mmol) at 0 °C. The reaction proceeded for 2 h. The white precipitate was removed by filtration through Celite, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate–hexanes (1:4) to afford **21a** (350 mg, 77%) as a white solid: mp 86–88 °C; $^1$H NMR δ 1.41–1.43 (d, *J* = 6.12, 3 H), 2.37–2.43 (dd, $J_1$ = 3.05, $J_2$ = 14.27, 1 H), 2.47, (s, 3 H), 2.91–2.96 (dd, $J_1$ = 6.51, $J_2$ = 14.28, 1 H), 4.06–4.11 (m, 1 H), 7.37–7.40 (d, *J* = 8.42, 2 H), 7.87–7.90 (d, *J* = 8.14, 2 H); IR (KBr) 2985, 1805, 1380, 1195, 1185, 760 cm$^{-1}$; $^{13}$C NMR δ 17.30, 21.41, 39.50, 55.33, 128.75, 129.71, 130.25, 146.14, 165.43; MS (CI with isobutanol) 256 ($MH^+$), 214, 155, 102. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.94; H, 5.33; N, 5.54.

**2-(Trimethylsilyl)ethyl 3-[1-(Tosyloxy)-2-oxo-4-azetidinyl]propionate (21c)** was prepared according to the same procedure as used for the synthesis of **21a**, starting with the corresponding *N*-hydroxy-β-lactam (335 mg, 1.29 mmol), TsCl (259 mg, 1.35 mmol), and $Et_3N$ (0.19 mL, 1.35 mmol) and was obtained as a colorless oil (479 mg, 90%). Because of its instability, this compound was partially characterized and was used for the next reaction immediately. $^1$H NMR δ 0.059 (s, 9 H), 0.98–1.03 (m, 2 H), 1.94–2.05 (m, 1 H), 2.22–2.29 (m, 1 H), 2.40–2.51 (m, 3 H), 2.48 (s, 3 H), 2.85–2.92 (dd, $J_1$ = 5.99, $J_2$ = 14.37, 1 H), 4.08–4.11 (m, 1 H), 4.16–4.22 (m, 2 H), 7.38–7.40 (d, *J* = 8.08, 2 H), 7.88–7.90 (d, *J* = 8.39, 2 H); IR (TF) 2955, 1800, 1760, 1595, 1180, 1250, 1180 cm$^{-1}$; $^{13}$C NMR δ −1.59, 17.24, 21.75, 27.14, 30.04, 37.87, 58.98, 62.95, 129.10, 129.94, 130.49, 146.39, 164.97, 172.30; MS 229 ($M^+ - CH_2 - SO_3C_6H_4CH_2$), 165, 149, 91.

***trans*-3-Azido-4-methyl-2-azetidinone (22a).** To a solution of *N*-hydroxy-4-methyl-2-azetidinone (**20**) (26 mg, 0.26 mmol) and diphenyl phosphoryl azide (0.07 mL, 0.29 mmol) in acetonitrile (1.0 mL) was added triethylamine (0.085 mL, 0.61 mmol). The reaction mixture was left for 36 h under nitrogen. The solvent was removed under reduced pressure, and the residue was purified by column chromatography with ethyl acetate–hexanes 1:2 to yield **22a** as a colorless oil (18 mg, 56%): $^1$H NMR δ 1.42–1.44 (d, *J* = 6.2, 3 H), 3.65–3.72 (dq, $J_1$ = 2.04, $J_2$ = 6.21, 1 H), 4.14–4.16 (t, *J* = 1.75, 1 H), 6.50 (b, 1 H); $^{13}$C NMR δ 19.24, 52.75, 70.80, 164.11; IR (TF) 3265, 2975, 2110, 1760, 1260 cm$^{-1}$; FAB 127 ($M^+$H). Anal. Calcd for $C_4H_6NO_4$: C, 38.09; H, 4.80. Found: C, 38.86; H, 4.99.

***trans*-3-Iodo-4-methyl-2-methyl-2-azetidinone (22b).** To a solution of **21a** (67 mg, 0.263 mmol) in acetonitrile (1.5 mL) was added $Et_3N$ (0.09 mL, 0.66 mmol) followed by TMSI (0.056 mL, 0.394 mmol). The reaction mixture was stirred at room temperature for 21 h. After concentration, the oily residue was purified by column chromatography with ethyl acetate–hexanes 1:2 to yield **22b** (28 mg, 51%) as a white solid: mp 65.5–68.5 °C; $^1$H NMR δ 1.41–1.43 (d, *J* = 6.17, 3 H), 3.94–4.01 (qd, $J_1$ = 6.02, $J_2$ = 1.82, 1 H), 4.48–4.49 (t, *J* = 1.94, 1 H), 5.93 (b, 1 H); $^{13}$C NMR δ 20.24, 20.99, 56.76, 165.10; IR (KBr) 3230, 2990, 1740, 1375, 1290 cm$^{-1}$. Anal. Calcd for $C_4H_6NOI$: C, 22.77; H, 2.87; N, 6.64. Found: C, 22.97; H, 2.61; N, 6.62.

***trans*-3-Bromo-4-methyl-2-azetidinone (22c)** was prepared according to the same procedure as used for the synthesis of compound **22b**, starting with **21a** (78 mg, 0.31 mmol), TMSBr (0.048 mL, 0.37 mmol), and $Et_3N$ (0.09 mL, 0.68 mmol) and was obtained as a colorless oil (22 mg, 44%): $^1$H NMR δ 1.44–1.46 (d, *J* = 6.23, 3 H), 3.89–3.96 (qd, $J_1$ = 6.25, $J_2$ = 1.91, 1 H), 4.36–4.38 (t, *J* = 1.99, 1 H), 6.09 (b, 1 H); $^{13}$C NMR δ 19.61, 48.90, 56.21, 163.80; IR (TF) 3260, 2980, 1760, 1375, 1210 cm$^{-1}$; MS *m/z* 122 ($^{81}$BrCHCHCH$_3$), 120 ($^{79}$BrCHCHCH$_3$), 69. Anal. Calcd for $C_4H_6NOBr$: C, 29.29; H, 3.69; N, 8.54. Found: C, 29.36; H, 3.80; N, 8.62.

***trans*-3-Chloro-4-methyl-2-azetidinone (22d).** To a solution of **21a** (60 mg, 0.24 mmol) and $(i\text{-Pr})_2$EtNH·Cl (194.7 mg, 1.2 mmol) in acetonitrile (1.0 mL) was added *N,N*-diisopropylethylamine (0.043 mL, 0.25 mmol). The reaction mixture was stirred at room temperature for 3 days and concentrated under reduced pressure. The residue was poured into water (1.0 mL), maintained at pH 6 with sulfuric acid, and extracted with ethyl acetate (3 × 1.0 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), concentrated, and purified by column chromatography with ethyl acetate–hexanes 1:2 to yield **22d** (13.7 mg, 49%) as a colorless oil: $^1$H NMR δ 1.45–1.47 (d, *J* = 6.27, 3 H), 3.80–3.87 (qd, $J_1$ = 6.33, $J_2$ = 1.93, 1 H), 4.33–4.34 (t, *J* = 2.00, 1 H), 6.09 (b, 1 H); $^{13}$C NMR δ 19.28, 56.35, 61.98, 163.55; IR (TF) 3280, 2985, 1775, 1385, 1355 cm$^{-1}$; MS 104 ($M^+$ − 15), 84, 78, 76 (base peak). HRMS Calcd for $C_3H_3NOCl$ ($M^+$ − 15): 103.99032. Found: 103.9908. Anal. Calcd for $C_4H_6NOCl$: C, 40.19; H, 5.06; N, 11.72. Found: C, 40.18; H, 5.12; N, 11.53.

***trans*-3-Acetoxy-4-methyl-2-azetidinone (22e).** To a solution of **21a** (60 mg, 0.24 mmol) and *N,N*-diisopropylethylammonium acetate (191 mg, 1.01 mmol) was added *N,N*-diisopropylethylamine (0.045 mL, 0.26

(25) (a) Loosemore, H. F.; Prat, R. F. *J. Org. Chem.* **1978**, *43*, 3611. (b) Wise, R.; Andrews, J. M.; Patel, N. *J. Antimicrob. Chemother.* **1981**, *7*, 531. (c) Kemp, J. D.; Closier, M. D.; Narayanaswami, S.; Stefaniak, M. H. *Tetrahedron Lett.* **1980**, *21*, 2991. (d) Sykes, R. B.; Bonner, D. P.; Bush, K.; Georgopapadakou, N. H. *Antimicrob. Agents Chemother.* **1982**, *21*, 85.

mmol). The reaction mixture was left at room temperature for 3 days and concentrated under reduced pressure. The residue was poured into water (2.0 mL) and the pH adjusted to 6 with sulfuric acid; extraction was done with ethyl acetate (3 × 1.0 mL). The combined organic solution was dried over $MgSO_4$ (anhydrous) and concentrated. The residue was further purified by column chromatography with ethyl acetate–hexanes 1:2 to yield **22d** (22.8 mg, 68%) as a colorless oil: $^1$H NMR δ 1.46–1.48 (d, $J$ = 6.23, 3 H), 2.15 (s, 3 H), 3.69–3.76 (qd, $J_1$ = 6.29, $J_2$ = 1.8, 1 H), 5.11–5.13 (t, $J$ = 1.95, 1 H), 6.00 (b, 1 H); $^{13}$C NMR δ 18.70, 20.42, 53.82, 81.55, 164.35, 182.96; IR (TF) 3280, 2980, 1775, 1750, 1375, 1235 cm$^{-1}$; MS 100 ($M^+$ – CONH), 58, 43. HRMS Calcd for $C_5H_8O_2$ ($M^+$ – CONH): 100.05243.

***trans*-3-(Thiophenoxy)-4-methyl-2-azetidinone (22f).** To a solution of **21a** (55 mg, 0.22 mmol) and thiophenol (0.033 mL, 0.33 mmol) in acetonitrile (1.0 mL) was added *N,N*-diisopropylethylamine (0.075 mL, 0.44 mmol). The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was purified by column chromatography with ethyl acetate–hexanes 1:2 to provide **22f** as a white solid (16 mg, 38%): mp 65–67 °C; $^1$H NMR δ 1.41–1.43 (d, $J$ = 6.12, 3 H), 3.59–3.65 (dq, $J_1$ = 2.28, $J_2$ = 6.14, 1 H), 3.92–3.93 (dd, $J_1$ = 1.34, $J_2$ = 2.13, 1 H), 7.30–7.54 (m, 5 H); $^{13}$C NMR δ 19.9, 52.7, 59.4, 127.9, 129.1, 132.4, 132.5, 166.3; IR (TF) 3260, 2965, 1755, 1580, 1480, 1435, 1375, 1345 cm$^{-1}$; MS 193 ($M^+$), 150, 135, 121, 105. HRMS Calcd for $C_{10}H_{11}NOS$: 193.0561. Found: 193.0554.

**2-(Trimethylsilyl)ethyl 3-(*trans*-3-azido-2-oxo-4-azetidinyl)propionate (22g)** was prepared according to the same procedure as used for the synthesis of compound **22b**, starting with **21c** (144.8 mg, 0.35 mmol), $TMSN_3$ (0.07 mL, 0.53 mmol), and $Et_3N$ (0.06 mL, 0.42 mmol) and was obtained as a colorless oil (62 mg, 62%): $^1$H NMR δ 0.04 (s, 9 H), 0.98–1.03 (m, 2 H), 2.00 (m, 2 H), 2.4 (t, $J$ = 7.0, 2 H), 3.57 (dt, $J_1$ = 2.2, $J_2$ = 6.5, 1 H), 4.18–4.22 (m, 2 H), 4.25 (t, $J$ = 1.5, 1 H), 6.45 (b, 1 H); $^{13}$C NMR δ −1.56, 17.33, 28.42, 30.82, 56.32, 63.26, 69.62, 163.97, 172.38; IR (TF) 3295, 2960, 2110, 1770, 1730, 1250, 1175, 860 cm$^{-1}$. HRMS Calcd for $C_{11}H_{20}N_4O_3Si$ ($M^+$ – 42): 256.1243. Found: 256.1244.

**2-(Trimethylsilyl)ethyl 3-(*trans*-3-Iodo-2-oxo-4-azetidinyl)propionate (22h).** To a solution of *N*-(tosyloxy)-β-lactam **21c** (25 mg, 0.061 mmol) and tetrabutylammonium iodide (26.82 mg, 0.073 mmol) in acetonitrile (0.5 mL) was added triethylamine (0.01 mL, 0.073 mmol). The reaction mixture was stirred at room temperature for 12 h. After concentration, the residue was purified by column chromatography with ethyl acetate–hexanes 1:2 to afford **22h** as a colorless oil (12 mg, 54%): $^1$H NMR δ 0.052 (s, 9 H), 0.97–1.03 (m, 2 H), 2.00–2.05 (m, 2 H), 2.39–2.44 (m, 2 H), 3.85–3.90 (dt, $J_1$ = 2.00, $J_2$ = 6.53, 1 H), 4.16–4.22 (m, 2 H), 4.55–4.57 (t, $J$ = 2.12, 1 H), 6.12 (b, 1 H); IR (TF) 3270, 2950, 1760, 1725, 1250, 1170, 1055 cm$^{-1}$. Anal. Calcd for $C_{11}H_{20}INO_3Si$: C, 35.8; H, 5.40; N, 3.79. Found: C, 36.00; H, 5.50; N, 3.89.

**2-(Trimethylsilyl)ethyl 3-(*trans*-3-(thiophenoxy)-2-oxo-4-azetidinyl)-propionate (22i)** was prepared according to the same procedure as used for the synthesis of compound **22f**, starting with **21c** (83 mg, 0.20 mmol), HSPh (0.03 mL, 0.3 mmol), and $Et_3N$ (0.084 mL, 0.60 mmol) and was obtained as a colorless oil (27 mg, 38%): $^1$H NMR δ 0.04 (s, 9 H), 0.95–1.00 (m, 2 H), 1.97–2.05 (m, 2 H), 2.31–2.36 (m, 2 H), 3.49–3.54 (dt, $J_1$ = 2.44, $J_2$ = 6.42, 1 H), 3.96–3.98 (dd, $J_1$ = 1.03, $J_2$ = 2.43, 1 H), 5.96 (b, 1 H), 7.31–7.34 (m, 3 H), 7.54–7.58 (m, 2 H); IR (TF) 3600, 2955, 1770, 1730, 1250, 860, 840 cm$^{-1}$; MS 308 ($M^+$ – CONH), 280, 171, 162, 158, 129, 73. HRMS Calcd for $C_{16}H_{24}O_3SiS$ ($M^+$ – CONH): 308.1266. Found: 308.1262.

**2-(Trimethylsilyl)ethyl 3-(*trans*-3-chloro-2-oxo-4-azetidinyl)propionate (22j)** was prepared according to the same procedure as used for the synthesis of compound **22b**, starting with **21c** (80 mg, 0.19 mmol), TMSCl (0.037 mL, 0.29 mmol), and $Et_3N$ (0.068 mL, 0.49 mmol) and was obtained as a colorless oil (27 mg, 50%): $^1$H NMR δ 0.051 (s, 9 H), 0.97–1.02 (m, 2 H), 2.02–2.07 (m, 2 H), 2.40–2.45 (t, $J$ = 7.14, 2 H), 3.71–3.76 (td, $J_1$ = 6.47, $J_2$ = 2.02, 1 H), 4.16–4.22 (m, 2 H), 4.41–4.42 (t, $J$ = 1.98, 1 H), 6.23 (b, 1 H); IR (TF) 3290, 2935, 1780, 1730, 1250, 860, 835 cm$^{-1}$; MS 236 ($M^+$ – CONH + 2), 234 ($M^+$ – CONH), 171, 158, 129, 75, 73. Anal. Calcd for $C_{11}H_{20}ClNO_3Si$: C, 47.56; H, 7.26; N, 5.04. Found: C, 47.71; H, 7.08; N, 5.03.

***N*-(Tosyloxy)-3-phthalimido-2-azetidinone (25).** According to Scheme I, **25** was synthesized from the corresponding *N*-phthalimido-D,L-serine. To a solution of *N*-phthalimido-D,L-serine (2.57 g, 10.94 mmol) and *O*-benzylhydroxylamine (1.48 g, 12.04 mmol) in methylene chloride (20 mL) was added a solution of DCC (2.48 g, 12.04 mmol) in methylene chloride (10 mL) at 0 °C. A large amount of precipitate was formed within 5 min. The reaction mixture was left at room temperature for 4 h and concentrated under reduced pressure. The residue was purified by column chromatography with ethyl acetate–hexanes 1:1 to provide *O*-benzyl *N*-phthalimido-D,L-serinylhydroxamate as a colorless oil (3.46 g, 94%): $^1$H NMR δ 3.24 (b, 1 H), 3.93 (b, 1 H), 4.19–4.24 (m, 1 H), 4.89 (b, 1 H), 4.93 (s, 2 H), 7.34–7.40 (m, 5 H), 7.75–7.77 (m, 2 H), 7.85–7.88 (m, 2 H), 9.28 (b, 1 H); $^{13}$C NMR δ 53.2, 60.4, 78.3, 123.6, 128.5, 128.7, 129.4, 131.5, 134.4, 134.8, 165.7, 168.0; IR (TF) 3460, 3300, 3080, 3060, 2960, 1770, 1720, 1680, 1390, 725 cm$^{-1}$; MS 340 ($M^+$), 218, 190, 173, 133, 104, 91. HRMS Calcd for $C_{18}H_{16}N_2O_5$: 340.1059. Found: 340.1054.

*O*-Benzyl *N*-phthalimido-D,L-serinylhydroxamate (3.46 g, 10.16 mmol) was dissolved in a mixture of acetonitrile (40 mL) and carbon tetrachloride (1.2 mL). To this solution were added triethylamine (1.7 mL, 12.19 mmol) and triphenylphosphine (2.93 g, 11.17 mmol) simultaneously. The reaction mixture was left overnight and then concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate–hexanes 1:2 to yield *O*-benzyl-*N*-hydroxy-3-phthalimido-2-azetidinone as white crystals (1.31 g, 40% from ethyl acetate–hexanes 1:2): mp 116–116.5 °C; $^1$H NMR δ 3.61–3.65 (t, $J$ = 5.19, 1 H), 3.74–3.76 (dd, $J_1$ = 4.55, $J_2$ = 2.58, 1 H), 5.08–5.11 (d, $J$ = 11.21, 1 H), 5.13–5.16 (d, $J$ = 11.25, 1 H), 5.18–5.21 (dd, $J_1$ = 5.40, $J_2$ = 2.52, 1 H), 7.39–7.78 (m, 5 H), 7.84–7.87 (m, 4 H); $^{13}$C NMR δ 50.2, 50.7, 78.2, 123.6, 128.6, 129.0, 129.2, 131.5, 134.5, 134.8, 160.7, 168.7; IR (KBr) 1795, 1775, 1715, 1400, 715 cm$^{-1}$; MS 278, 215, 187, 173, 148, 130, 117, 104, 91, 76. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.21; H, 4.52; N, 8.58.

*O*-Benzyl-*N*-hydroxy-3-phthalimido-2-azetidinone (99 mg, 0.31 mmol) was dissolved in methanol (15 mL). The resultant solution was subjected to hydrogenolysis for 2 h to provide *N*-hydroxy-3-phthalimido-2-azetidinone (66 mg, 0.28 mmol, 92.5%), which was dissolved in acetonitrile (1 mL). *p*-Toluenesulfonyl chloride (54.2 mg, 0.28 mmol) was added to the above solution followed by triethylamine (0.04 mL, 0.28 mmol). The reaction mixture was stirred at room temperature for 2 h. The white precipitate was removed by filtration, and the clear filtrate was concentrated under vacuum. The product was purified by column chromatography with ethyl acetate–hexanes 1:2 to afford a white solid (101 mg, 92%): mp 102–103 °C; $^1$H NMR δ 2.48 (s, 3 H), 4.09–4.12 (dd, $J_1$ = 5.02, $J_2$ = 6.03, 1 H), 4.18–4.21 (dd, $J_1$ = 3.24, $J_2$ = 4.95, 1 H), 5.33–5.36 (dd, $J_1$ = 3.24, $J_2$ = 6.09, 1 H), 7.44–7.46 (d, $J$ = 8.02, 2 H), 7.78–7.91 (m, 4 H), 8.05–8.08 (d, $J$ = 8.42, 2 H); $^{13}$C NMR δ 21.9, 50.6, 52.1, 123.9, 129.5, 120.1, 130.4, 131.5, 134.7, 146.7, 161.3, 166.4; IR (KBr) 2980, 1795, 1720, 1400, 1200, 715 cm$^{-1}$; MS 214 ($M^+$ – $HOSO_2C_6H_4CH_3$), 186, 172, 132, 104, 91, 76. HRMS Calcd for $C_{18}H_{14}N_2O_6S$ ($M^+$ – $HOSO_2C_6H_4CH_3$): 214.03784. Found: 214.0383.

**3-Azido-3-phthalimido-2-azetidinone (26)** was prepared according to the same procedure as used for the synthesis of compound **22b**, starting with **25** (45 mg, 0.117 mmol), $TMSN_3$ (0.023 mL, 0.176 mmol), and $Et_3N$ (0.02 mL, 0.140 mmol) and was obtained as a white solid (18 mg, 60%): mp 164 °C (dec); $^1$H NMR δ 3.77–3.79 (d, $J$ = 6.90, 1 H), 4.09–4.11 (d, $J$ = 6.87, 1 H), 6.19 (b, 1 H), 7.80–7.82 (m, 2 H), 7.92–7.94 (m, 2 H); IR (KBr) 3325, 2220, 1805, 1755, 1720, 1460, 1355, 1335, 1235, 1150, 720 cm$^{-1}$; MS 229 ($M^+$ – 28), 214, 186, 167, 149, 132, 104 (base peak). HRMS Calcd for $C_{11}H_7N_3O_3$ ($M^+$ – 28): 229.04874. Found: 229.0489.

**3-Methoxy-3-phthalimido-2-azetidinone (27).** To a solution of **25** (72 mg, 0.19 mmol) in a mixture of acetonitrile (0.5 mL) and methanol (0.5 mL) was added triethylamine (0.029 mL, 0.21 mmol). The resultant mixture was stirred at room temperature for 14 h. The solvents were evaporated, and the residue was purified by column chromatography with ethyl acetate–hexanes 1:1 to afford **27** (17 mg, 37%) as white solids: $^1$H NMR δ 3.61 (s, 3 H), 3.86–3.88 (d, $J$ = 6.68, 1 H), 3.97–3.99 (d, $J$ = 6.63, 1 H), 6.04 (b, 1 H), 7.78–7.81 (m, 2 H), 7.91–7.94 (m, 2 H); IR (KBr) 3340, 1800, 1750, 1720, 1375, 720 cm$^{-1}$; MS 246 ($M^+$), 203, 175, 161, 147, 132, 130, 104 (base peak), 76. HRMS Calcd for $C_{12}H_{10}N_2O_4$: 246.06406. Found: 246.0643.

***trans*-3-Methoxy-4-methyl-2-azetidinone (28).** To a solution of **21a** (72 mg, 0.28 mmol) in a mixture of acetonitrile (0.5 mL) and methanol (0.5 mL) was added triethylamine (0.047 mL, 0.34 mmol). This reaction mixture was left at room temperature for 7 days. The solvents were evaporated, and the oily residue was purified by column chromatography with ethyl acetate–hexanes 1:2 followed by 1:1 to provide **28** as an oily compound (2.5 mg, 8% based on consumed **21a**) along with **21a** (14 mg): $^1$H NMR δ 1.38–1.40 (d, $J$ = 6.22, 3 H), 3.53 (s, 3 H), 3.71–3.78 (dq, $J_1$ = 1.47, $J_2$ = 5.91, 1 H), 4.14–4.15 (t, $J$ = 1.92, 1 H), 5.90 (b, 1 H); IR (TF) 3300, 2940, 1755, 1450, 1375 cm$^{-1}$; FAB 116 ($M^+$H).

***trans*-3-(Triethylammonium)-4-methyl-2-azetidinone Tosylate (30).** To a solution of **21a** (91 mg, 0.36 mmol) and bis(trimethylsilyl)acetamide (0.13 mL, 0.54 mmol) in acetonitrile (0.75 mL) was added triethylamine (0.055 mL, 0.4 mmol). The reaction mixture was left at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue was poured into water (2 mL). The aqueous solution was extracted with ethyl acetate (3 × 2.0 mL) and concentrated to dryness to afford **30** as viscous liquid (90%, as determined by $^1$H NMR of crude reaction mixture): $^1$H NMR δ 1.34–1.38 (t, $J$ = 7.35, 9 H), 1.46–1.48

(d, $J$ = 5.9, 3 H), 2.35 (s, 3 H), 3.65-3.58 (m, 6 H), 4.47-4.44 (dq, $J_1$ = 5.99, $J_2$ = 2.12, 1 H), 4.47 (s, 1 H), 7.18-7.16 (d, $J$ = 7.93, 2 H), 7.77-7.75 (d, $J$ = 8.10, 2 H), 8.58 (b, 1 H); IR (TF) 1770, 1500, 1440, 1250 cm$^{-1}$; FAB (cation) 185 ($M^+$), 142 ($M^+$ - 43).

**3-(3-Bromo-4-methyl-2-oxoazetidinyl)-2-butenamide (32).** To a solution of **21a** (94 mg, 0.369 mmol) and tetrabutylammonium bromide (237.5 mg, 0.738 mmol) in acetonitrile (1.5 mL) was added $Et_3N$ (0.05 mL, 0.369 mmol). The reaction mixture was left for 44 h at room temperature and concentrated. The residue was poured into water (2 mL) and extracted with ethyl acetate (3 × 2 mL). The organic layers were combined, dried, and concentrated. The residue was purified by column chromatography with ethyl acetate-hexanes 1:2 to provide **32** (19 mg, 22%) and **22c** (13 mg, 22%) as oily compounds. Compound **32**: $^1$H NMR $\delta$ 1.58-1.60 (d, $J$ = 6.30, 3 H), 2.01 (s, 3 H), 4.14-4.30 (dq, $J_1$ = 2.34, $J_2$ = 6.24, 1 H), 4.30-4.31 (t, $J$ = 2.36, 1 H), 5.03 (b, 1 H), 5.49 (s, 1 H), 8.76 (b, 1 H); IR (TF) 3420, 3305, 2980, 1775, 1630, 1540, 1310, 1235, 830 cm$^{-1}$; $^{13}$C NMR $\delta$ 18.17, 46.68, 58.20, 86.63, 146.33, 161.12, 163.64; MS 248 ($M^+$ + 2), 246 ($M^+$), 155, 126, 84 (base peak). HRMS Calcd for $C_8H_{11}N_2O_2Br$: 246.00039. Found: 246.0001.

**3-[3-[[2-(Trimethylsilyl)ethoxy]carbonyl]propyl]-3-[3-chloro-4-[3-[[2-(trimethylsilyl)ethoxy]carbonyl]propyl]-2-oxoazetidinyl]propenamide (31)** was prepared according to the same procedure as used for the synthesis of compound **32** and obtained as a colorless oil (32%) alone with **22j** (8%). Compound **31**: $^1$H NMR $\delta$ 0.044 (s, 9 H), 0.046 (s, 9 H), 0.97-1.03 (m, 4 H), 1.97-2.06 (m, 1 H), 2.48-2.61 (m, 7 H), 0.99-4.04 (dq, $J_1$ = 8.65, $J_2$ = 2.06, 1 H), 4.15-4.23 (m, 4 H), 4.45-4.46 (d, $J$ = 2.43, 1 H), 5.45 (s, 1 H), 5.85 (b, 1 H), 8.69 (b, 1 H); IR (TF) 3440, 3320, 2970, 1790, 1730, 1630, 1550, 1330, 1255, 1180, 865, 840 cm$^{-1}$; MS 518 ($M^+$), 266, 221, 193, 178, 106, 91. HRMS Calcd for $C_{22}H_{39}N_2O_6Si_2Cl$: 518.20352. Found: 518.2035.

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# Photolysis of Tp'Rh(CN-neopentyl)($\eta^2$-PhN=C=N-neopentyl) in Alkanes and Arenes: Kinetic and Thermodynamic Selectivity of [Tp'Rh(CN-neopentyl)] for Various Types of C-H Bonds

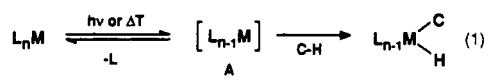
**William D. Jones* and Edward T. Hessell**

*Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627.* *Received April 17, 1992*

**Abstract:** Irradiation of the carbodiimide complex [HB(3,5-dimethylpyrazolyl)$_3$]Rh(CNR)(PhN=C=NR) (R = neopentyl) in benzene, toluene, mesitylene, cyclopentane, cyclohexane, propane, or pentane solvent leads to both the clean elimination of the carbodiimide ligand and the formation of the C-H oxidative addition product [HB(3,5-dimethylpyrazolyl)$_3$]Rh(CNR)(R')H. These products have been isolated as their chloride derivatives. Methane can be activated by exchange with the cyclohexyl derivative. The *n*-pentyl derivative [HB(3,5-dimethylpyrazolyl)$_3$]Rh(CNR)(*n*-pentyl)Cl crystallizes in monoclinic space group $P2_1/c$ with $a$ = 8.8865 (28) Å, $b$ = 11.8016 (30) Å, $c$ = 31.4597 (14) Å, $\beta$ = 90.727 (22)°, $Z$ = 4, and $V$ = 3098 (2) Å$^3$. Competitive studies show that both benzylic and aromatic C-H bonds react under conditions of kinetic control but that the aromatic activation products are thermodynamically preferred. Activation of primary alkane C-H bonds is preferred over secondary activation. This complex is found to be more selective than either [Cp*Rh(PMe$_3$)] or [Cp*Ir(PMe$_3$)]. The rates of reductive elimination of *n*-pentane, cyclopentane, cyclohexane, mesitylene, methane, and benzene have been measured and are used to establish relative Rh-R bond strengths for these ligands.

## Introduction

The activation of C-H bonds by homogeneous transition-metal complexes continues to be an active area of research, and stable transition-metal activation products are now known for a number of systems.[1,2] The process leading to such products usually involves the photochemical or thermal generation of a high-energy coordinatively unsaturated intermediate (eq 1), which then inserts




into the C-H bond of an alkane. The insertion step can be viewed mechanistically as being similar to carbene insertion.[3,4] Much is known about the relative thermodynamic stabilities of various products derived from the oxidative addition of C-H bonds to unsaturated metal centers[5] ($\Delta G°$ of Figure 1) and, in turn, the relative strengths of the metal-carbon bonds in such products.[6]

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