J|A|C|S
COMMUNICATIONS

Published on Web 09/09/2003

Dynamic Kinetic Asymmetric Cycloadditions of Isocyanates to Vinylaziridines

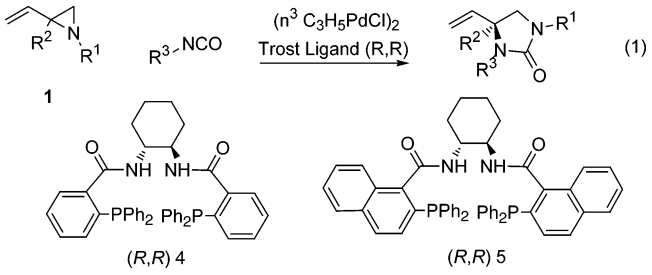
Barry M. Trost* and Daniel R. Fandrick

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received July 21, 2003; E-mail: bmtrost@stanford.edu

The dynamic kinetic asymmetric transformations (DYKATs) of racemic compounds in simple addition reactions provide an efficient and atom economic synthesis of useful chiral compounds.[1] In particular, the highly enantioselective addition of alcohols, amines, phthalimide, and acetoacetates to vinyl epoxides has recently been reported with the Trost ligands **4** and **5**.[2] Although aziridines are normally considerably less reactive toward nucleophilic additions, their successful reaction with isocyanates in the presence of Pd(O)[3−5] led us to consider their ability to function in a DYKAT process (eq 1). To obtain asymmetric induction for the palladium-catalyzed DYKATs of vinylaziridines, the interconversion of the diastereomeric π-allyl palladium intermediates via a $\eta^3-\eta^1-\eta^3$ interconversion must occur faster than the subsequent nucleophilic addition and be under Curtin−Hammett conditions. To initiate this methodology, we chose isocyanates as the addition component to circumvent regioselectivity issues.

Initial experiments were preformed with the parent aziridine ($R^1 = CH_2C_6H_5$, $R^2 = H$) and phenyl isocyanate using conditions analogous to those of Alper et al.[3c] (eq 1). Using 4 mol % $Pd(OAc)_2$ and 10 mol % (*R*,*R*) **4** in degassed THF at ambient temperature, we synthesized the corresponding imidazolidinone in 29% yield and a modest 59% ee after 24 h. After optimization of the palladium precatalyst, ligand, and solvent, the yield can be increased to 98% with still a modest 41% ee using 2 mol % $(\eta^3\text{-}C_3H_5PdCl)_2$ and 6 mol % (*R*,*R*) **5** in degassed methylene chloride for 2 h at room temperature. Additionally, variation of the temperature, concentration, or solvent showed little improvement on the enantioselectivity, but at least 2 mol % $(\eta^3\text{-}C_3H_5PdCl)_2$ was necessary for complete conversion on a 1 mmol scale.



(1)

The low enantioselectivity was attributed to the nucleophilic addition competing with the rapid interconversion of the π-allyl palladium intermediates. Halide additives have been shown to increase the rate of this interconversion and lead to higher enantioselectivities for the DYKAT of epoxides.[2] Addition of 4−10 mol % TBAT (tetrabutylammonium triphenyl-difluorosilicate) to reaction 1 initially increased the enantiomeric excess to ∼70% at 5 °C with 2 mol % $(\eta^3C_3H_5PdCl)_2$ and 6 mol % (*R*,*R*) **5** in degassed THF after 24 h. Using different sources of TBAT led to irreproducibility of the results. Water may have contaminated the acid-sensitive TBAT[6] and in the presence of isocyanates furnished an acidic solution. Experiments were performed with several tertiary amine bases at various quantities in addition to TBAT and showed little effect on the enantioselectivity disfavoring the decomposition of TBAT as the source of the irreproducibility. On the other hand, the adventitious water leading to acidic conditions may have influenced the enantioselectivity. Therefore, we studied the effect of an acid and a halide additive (Table 1).

Table 1. Representative Additive Effect for *N*-Benzylvinylaziridine[a]

entry	additive (pK_a in H_2O[7])	time[b]	conv[c]	yield[d]	ee[e]
1	none	2 h	100%	98%	41%
2[f]	none	20 h	83%	62%	43%
3[f]	4% TBAT	4 h	100%	73%	35%
4[f]	4% THACl	30 h	83%	42%	43%
5	6% pivalic acid (5.0)	2 h	100%	98%	77%
6	6% AcOH (4.8)	2 h	100%	99%	80%
7	10% AcOH (4.8)	2 h	100%	99%	82%
8	6% formic acid (3.8)	2 h	100%	98%	77%
9	6% TFA (0.5)	4 h	∼98%	84%	70%
10	12% HOBt (4.6)	2 h	100%	96%	81%
11	10% HOAt (3.5)	2 h	100%	ND	72%
12	10% TBAOAc	20 h	∼50%	ND	11%

[a] Reactions were conducted with aziridine ($R^1 = CH_2C_6H_5$, $R^2 = H$), 2 mol % $(\eta^3\ C_3H_5PdCl)_2$, 6 mol % **5**, 0.12 M in CH_2Cl_2, 1 equiv of PhNCO at room temperature. [b] Time until complete consumption of aziridine or until the indicated time. [c] Conversion based on ratio of product to SM by ^1H NMR. [d] Isolated yield. [e] ee determined by chiral HPLC. [f] Reactions conducted in THF. ND = Not determined. TFA = Trifluoroacetic acid. HOAt = 1-Hydroxy-7-azabenzotriazole. HOBt = 1-Hydroxybenzotriazole. TBAOAc = Tetrabutylammonium acetate. THACl = Tetrahexylammonium chloride.

Contrary to other Pd-AAA reactions requiring Curtin−Hammett conditions, halide ions had little, if any, effect (entries 3 and 4), and carboxylate had a deleterious effect (entry 12). On the other hand, acid additives had a dramatic effect (entries 5−11). The effect seems to be dependent upon the pK_a, which, if translated to an aqueous medium, would correspond to approximately 4.7. Varying acetic acid from 4 to 25 mol % demonstrated that 8 or more mol % acetic acid was necessary for optimal enantioselectivity. Addition of acyl transfer catalysts such as DMAP showed no effect on the enantioselectivity with or without acetic acid. More interestingly, HOBt (entry 10) was as effective as acetic acid, and HOAt (entry 11) was somewhat inferior. It appears then that the role of HOBt is more related to its pK_a than to its ability to promote acyl transfer. In accord with this interpretation, the more acidic HOAt gave lower ee's. A reasonable rationalization relates to the requirement that equilibration of the diastereomeric π-allyl palladium intermediates must be faster than cyclization to achieve high ee in a DYKAT. By protonation of the nitrogen upon opening of the aziridine which should slow its rate of addition to the isocyanate or the nitrogen of the initial adduct between the ring opened aziridine and the isocyanate which slows the cyclization rate, an $\eta^3-\eta^1-\eta^3$ interconversion of the π-allyl palladium intermediates can compete effectively with product formation. Thus, a Curtin−Hammett situation is created wherein the enantiodiscriminating event is the cyclization.

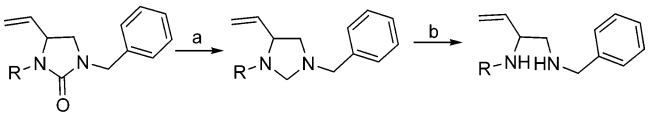
10.1021/ja037450m CCC: $25.00

Table 2. Isocyanate and Aziridine Effect on Eq 1[a]

entry	R^1	R^2	R^3	ee %[b] (yield %[c])
1	$CH_2C_6H_5$	H	Ph	82 (99)
2[d]	$CH_2C_6H_5$	H	COC_6H_5	13 (94)
3[f]	$CH_2C_6H_5$	H	p-$CH_3OC_6H_4$	90 (99)
4[e]	$CH_2C_6H_5$	H	$CH_2C_6H_5$	95 (98)
5[e]	$CH_2C_6H_5$	H	o,p-$(CH_3O)_2C_6H_3$	91 (96)
6	$CH_2C_6H_5$	H	p-$CH_3SC_6H_4$	85 (85)
7	$CH_2C_6H_5$	CH_3	Ph	80 (60)
8	o-$NO_2C_6H_4CH_2$	H	Ph	83 (99)
9	o-$NO_2C_6H_4CH_2$	H	p-$CH_3OC_6H_4$	82 (99)
10[e]	p-$CH_3OC_6H_4$	H	Ph	74 (52)
11	tosyl	H	Ph	65 (61)

[a] Reactions were conducted with 2 mol % (η^3 $C_3H_5PdCl)_2$, 6 mol % **5** (*R*,*R*), 10 mol % AcOH, 1 equiv of of isocyanate, and 0.12 M in CH_2Cl_2 for 2 h. [b] ee determined by chiral HPLC. [c] Isolated yield. [d] 8 h. [e] 18 h. [f] Reaction was conducted with 1 mol % (η^3 $C_3H_5PdCl)_2$, 3 mol % **5** (*R*,*R*), 5 mol % AcOH, 1 equiv of isocyanate, and 0.24 M in CH_2Cl_2.

Scheme 1. Conversion of Imidazolidinones to Diamines[a]



6a: R=Ph **7a**: R = Ph **8a**: R = Ph
6b: R=$CH_2C_6H_5$ **7b**: R = $CH_2C_6H_5$ **8b**: R = $CH_2C_6H_5$

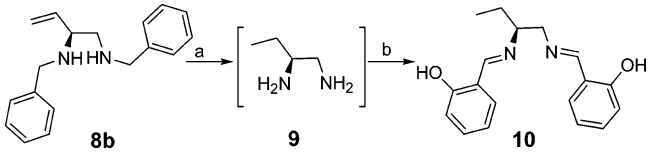
[a] Reagents and conditions: (a) $LiAlH_4$, Et_2O, reflux 2−20 h. (b) $H_2NOH{\cdot}HCl$, 0.01% HCl aq 60 °C, 1 h (**8a** 91%, **8b** 94% for two steps).

Having developed highly enantioselective conditions for the DYKAT of vinylaziridines, we examined the scope of the substrate and isocyanate (Table 2). Generally, the cycloaddition furnished the chiral imidazolidinone in high yield and enantiomeric excess with electron-rich isocyanates. The enantioselectivity correlated with the electrophilicity of the isocyanate. With the parent aziridine, the enantiomeric excess ranged from 13% with benzoyl isocyanate to 95% with benzyl isocyanate (entries 1−6). Similarly, the more electron-rich *p*-anisyl isocyanate (entry 3) gave higher ee's than phenyl isocyanate (entry 1). Substituents at the 2 position of the vinyl aziridine, or ortho position of the benzyl moiety, and *N*-aryl aziridine are all well tolerated in the DYKAT (entries 7−10). The enantioselectivity was dramatically lower for *N*-tosyl aziridine (entry 11) than the parent aziridine. Interestingly, a tetrasubstituted carbon by using a 1,1-disubstituted aziridine (entry 7) was created in about the same ee as that for the parent vinylarizidine (entry 1), although the reaction was somewhat less efficient as was reflected by the lower yield.

Imidazolidinones **6** were efficiently converted to their corresponding diamines **8** through the transformations shown in Scheme 1. LAH reduction provided the sensitive imidazolidines in high yield. Typical hydrolyses utilize strong aqueous acidic conditions that are not compatible with *N*-aryl or *N*-benzyl substituents.[8,9] The hydrolysis with hydroxylamine[10] in weakly acidic conditions enables the conversion to the diamines in >90% yield for the two steps.

The absolute configuration of the imidazolidinones was established by conversion of **8b** to the known SALEN ligand **10** (Scheme 2). The filtrate of the hydrogenation and hydrogenolysis of **8b** (95% ee from **6b**) was directly subjected to salicyaldehyde to yield **10** in reasonable purity with an $[\alpha]^{27}_D = +174$ ($c = 0.66$ in $CHCl_3$) (lit[11] $[\alpha]_D = +223$ ($c = 0.72$ in $CHCl_3$)) to establish the absolute configuration for imidazolidin-2-one **6b** as (*S*). By analogy, the absolution configurations of the imidazolidinones in entries 1 and 3−11 (Table 2) were assigned accordingly.

Scheme 2. Conversion of Imidazolidinone **8b** to a SALEN Ligand[a]



8b **9** **10**

[a] Reagents and conditions: (a) $Pd(OH)_2/C$, 85 psi H_2, MeOH, 26 h. (b) Salicylaldehyde, MeOH, reflux 2 h (~60% for two steps).

In summary, these reactions report the first examples of the asymmetric cycloaddition of isocyanates to vinyl aziridines. High yields and enantioselectivity can be obtained for a broad array of imidazolidin-2-ones through simple addition reactions. Also, chiral diamines can be efficiently synthesized from the imidazolidin-2-ones.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute (GM-13598) for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility of the University of California-San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Full experimental procedures, synthesis of aziridines, and characterization data for all unknown compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705. (c) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14.
(2) (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702−12703. (b) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713−1716. (c) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968−5976. (d) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907−12908.
(3) (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999−1015. (b) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91−92. (c) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887−5890.
(4) For cycloadditions of enantiomerically pure vinyl aziridines, see: Baeg, J.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700−4701.
(5) For related asymmetric cycloadditions of isocyanates to vinyl epoxides with modest enantioselectivities, see: Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709−3715.
(6) Handy, C. J.; Lam, Y.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542−3543.
(7) (a) *CRC Handbook of Chemistry and Physics*, 83rd ed.; CRC Press LLC: New York, 2002; 8-46−8-49. (b) Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L.; Ragnarsson, U. *J. Chem. Res., Miniprint* **1993**, *11*, 3008−3028.
(8) (a) Toja, E.; Ferrari, P.; Tarzia, G. *Heterocycles* **1987**, *26(8)*, 2129−2139. (b) Kavrakova, I. K.; Lyapova, M. J. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1580−1586. (c) Keyserlingk, N. G.; Martens, J. *Eur. J. Org. Chem.* **2002**, 301−308.
(9) King, H. *J. Chem. Soc.* **1920**, *117*, 988−992.
(10) (a) Nezbedova, L.; Drandarov, K.; Werner, C.; Hesse, M. *Helv. Chim. Acta* **2000**, *83*, 2953−2960. (b) Guggisberg, A.; Drandarov, K.; Hesse, M. *Helv. Chim. Acta* **2000**, *83*, 3035−3042.
(11) Choi, J. Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37(43)*, 7795−7796.

JA037450M