Diastereoselective Three Component Reaction of *N*-glyoxyloyl Camphorpyrazolidinone, Amine and Allyltributylstannane: Facile Synthesis of Homoallylic Amines

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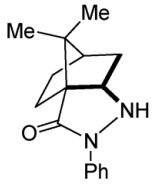
Diastereoselective allylation of imine derived from *N*-glyoxyloyl camphorpyrazolidinone and amines was treated with allyltributylstannane in the presence of triflic acid. The corresponding optically enriched homoallylic amines were obtained in reasonable to high material yields and with practical levels of stereoselectivity in 10 min at ambient temperature.

Keywords: Diastereoselective; Chiral auxiliary; Allylation; Homoallylic amine; Stereoselectivity; Camphorpyrazolidinone.

INTRODUCTION

Allylation of carbonyls and imines constitutes one of the most useful carbon-carbon bond formations for the construction of homoallylic alcohols and amines.[1] Generally, allylation of the low reactive aldimines is carried out using allyltributylstannane or other allyllic reagents in the presence of a Lewis acid such as $TiCl_4$, $PdCl_2(PPh_3)_2$, BF_3, $LiClO_4$, $La(OTf)_3$ to give the desired product.[2] A one-pot three-component strategy is a convenient and attractive approach for homoallylic amines preparation.[3] Several drawbacks that are encountered with the current methods include long reaction time, unsatisfactory material yields, require the use of additives, etc. In addition, the stereoselective three component reaction of the carbonyl derivative, amine and allyl reagent has not yet been extensively investigated.[4] We wish to report here an efficient diastereoselective allylation of imine, derived from the reaction of *N*-glyoxyloyl camphorpyrazolidinone **2** and amines, with allyltributylstannane in the presence of triflic acid. Reasonable to high material yields and a practical level of diastereoselectivities are obtained in 10 min at ambient temperature.



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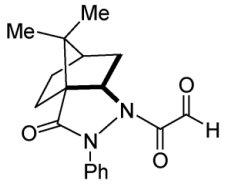

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RESULTS AND DISCUSSION

The starting camphorpyrazolidinone (**1**) was designed and synthesized in this laboratory and has proven to be an efficient chiral auxiliary in asymmetric synthesis.[5] The starting *N*-glyoxyloyl camphorpyrazolidinone (**2**) can be readily prepared from **1** in a two-step reaction as previously reported.[6] No desired product was observed when **2** was treated with *p*-anisidine and allyltributylstannane in the absence of a catalyst (Table 1, entry 1). The use of lanthanide triflates to catalyze the aldimine formation from aldehyde and amine has been reported.[7] We then examined various lanthanide triflates in this reactions. The use of $La(OTf)_3$, $Yb(OTf)_3$, $Eu(OTf)_3$ in THF at ambient temperature provide the desired product in 52-72% yield and over 80% de (entries 2-4). For the *N*-glyoxyloyl camphorpyrazolidinone derived three-component reaction, only trace amounts of homoallylic alcohol (< 5%) were identified. The structure of the desired homoallylic amine was assigned by ^{1}H-, ^{13}C-NMR, and HRMS analyses. The diastereoselectivity was determined by HPLC analysis of the crude products, and the absolute stereochemistry was assigned by single crystal X-ray analysis.[8] The C-2 methine proton (camphor numbering) of the major (*S*)-3 was found to be 4.10 ppm in the ^{1}H NMR spectrum while the minor (*R*)-3 appeared as 3.87 ppm. This is due to the anisotropic effect of the *p*-anisidine benzene ring shields of the C-2 methine in (*R*)-3. The reactivity decreased when $Sn(OTf)_2$ was used with comparable stereoselectivity (entry 6). The use of $Zn(OTf)_2$

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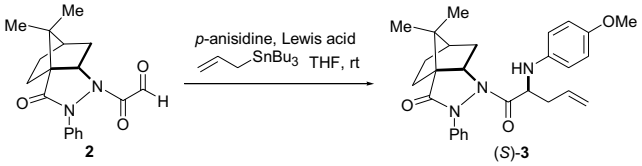
Table 1. Three-component diastereoselective allylation reaction in THF[a]



Entry	Additive	t/(h)	yield (%)[b]	% de[c]
1	-	4 d	0	-
2	$La(OTf)_3$	30	72	82
3	$Yb(OTf)_3$	7	60	88
4	$Eu(OTf)_3$	4	52	85
5	$Sc(OTf)_3$	4	50	89
6	$Sn(OTf)_2$	4	44	88
7	$Zn(OTf)_2$	2 d	72	28
8	Ag(OTf)	1 d	60	75
9	Tf_2O	1/6	68	88
10	TfOH	1/6	81	85

[a] Unless otherwise noted, all reactions were carried out at ambient temperature using **2** (0.16 mmol), *p*-anisidine (1.1 equiv), allyltributylstannane (1.2 equiv), Lewis acid (1.0 equiv) in THF.
[b] Total isolated yield.
[c] Diastereomeric ratios was determined by HPLC analysis of the crude products (Daicel chiralcel chiral OD column: 2-propanol/hexane = 15:85, 1.0 mL/min; t_R = 23.2 min; t_S = 42.0 min.).

and Ag(OTf) further decreased the reactivity (entries 7-8). To our surprise, the reactivity was significantly improved when Tf_2O was used in the reaction (entry 9). Finally, the product was obtained in 10 min with 81% material yield and 85% de when TfOH was used (entry 10). The protic acid TfOH turned out to be an efficient catalyst for the three-component coupling.

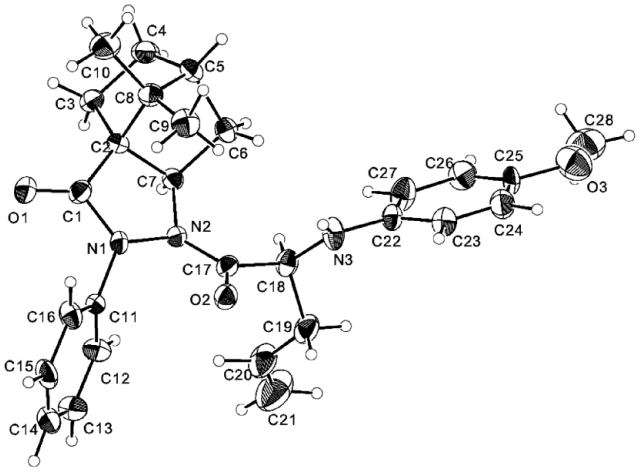


Fig. 1. X-ray ORTEP drawing of (*S*)-3.

Table 2. Solvent and temperature effects of the diastereoselective allylation

Entry	Solvent	Temp (°C)	t/h	Yield (%)	% de
1	CH_2Cl_2	rt	1/6	73	60
2	CH_3CN	rt	1/6	76	52
3	MeOH	rt	1	65	66
4	toluene	rt	3	71	72
5	THF	0	1	82	88
6	THF	-25	3	75	92
7	THF	-78	3	54	94

The solvent and temperature effects were then investigated under the optimized reaction conditions. The use of various organic solvents (CH_2Cl_2, CH_3CN, MeOH and toluene) failed to improve the results (Table 2, entries 1-4). The THF turned out to be the solvent of choice for this reaction. The stereoselectivity increased when the reaction was carried out at low temperature. The diastereoselectivity was improved slightly to 88% de at 0 °C and further raised to 92 and 94% de at -25 and -78 °C, respectively (entries 5-7).

To test the feasibility of the imine allylation, various primary amines were examined in the reaction. The use of aniline affords the desired product with 85% chemical yield and 86% de in 10 min under the optimum reaction conditions. Comparable material yield and stereoselectivity (78% and 82% de) are obtained when *p*-chloroaniline is used. Both the reactivity and stereoselectivity decreased (61% and 52% de) when benzylamine was used in 24 h. The use of simple aliphatic amines failed to react with the *in situ* generated aldimine under the same reaction conditions. This is probably because alkylimine is energetically less stable than is arylimine, and this prevent the formation of aldimine.

The stereochemical bias of the present study is unclear at this moment and can be proposed as follows. The initial formed α-imino amide may adopt the energetically favored *s-trans* conformation with the amide group toward the pyrazolidinone phenyl group.[5h] The addition of the TfOH shifts the equilibrium toward the *s-cis* five-membered ring conformation in the transition state. The activated allylating reagent attacks from the *si* face of the imino carbon center to give the desired stereoisomer (Fig. 2).[9]

In summary, the diastereoselective three-component coupling of *N*-glyoxyloyl camphorpyrazolidinone, amine and tributylallylstannane has been developed for the synthesis of homoallylic amine with high chemical yield and

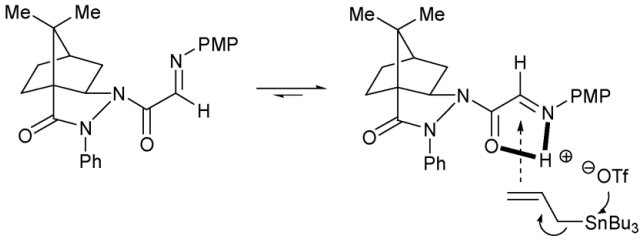


Fig. 2. Proposed mechanism of the three-component coupling allylation.

stereoselectivity. This extends the versatile and general utility of the camphor derived *N*-glyoxyloyl camphorpyrazolidinone. Further synthetic applications are currently underway.

EXPERIMENTAL

All reagents were used as purchased from commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were recorded on a Finnigan TSQ-700 at an ionizing energy of 70 eV and HRMS spectra were recorded on a Jeol SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure with a rotary evaporator, and the residue was purified by flash column chromatography on silica gel (230-400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions.

Typical procedure of the three component one-pot reaction

To a solution of *N*-glyoxyloyl camphorpyrazolidinone **2** (50 mg, 0.16 mmol) in THF (3 mL) was added *p*-anisidine (24 mg, 0.19 mmol), tributylallylstannane (55 μL, 0.18 mmole) and triflic acid (15 μL, 0.17 mmole) at ambient temperature for 10 min. The reaction mixture was diluted with aqueous sat. $NaHCO_3$ (5 mL) and extracted with dichloromethane (2 × 10 mL). The organic layer was separated and dried over anhydrous $MgSO_4$, concentrated and flash column chromatography was used to give the desired homoallylic amine **3** as a white solid in 81% yield.

(*S*)-**3**: R_f = 0.21 (hexanes:EtOAc = 3:1), ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.27-7.24 (m, 2H), 7.24-7.15 (m, 3H), 7.10-7.08 (m, 2H), 6.78 (d, *J* = 8.76 Hz, 2H), 6.60 (d, *J* = 8.44 Hz, 2H), 5.89-5.70 (m, 1H), 5.15-5.11 (m, 1H), 4.11-4.06 (m, 2H), 3.75 (s, 3H), 2.78-2.65 (m, 1H), 2.46-2.43 (m, 2H), 2.29-2.20 (m, 1H), 2.20-2.10 (m, 1H), 2.09-1.97 (m, 2H), 1.42-1.35 (m, 2H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 170.4, 153.5, 139.9, 138.3, 133.14, 128.3, 125.8, 121.74, 118.7, 117.3, 114.7, 66.1, 59.0, 57.4, 55.6, 53.4, 46.4, 38.7, 36.3, 28.3, 26.7, 20.1, 20.0; HRMS *m/z* 459.2527 (calcd for $C_{28}H_{33}N_3O_3$: 459.2516), Crystal data at 200(2) K: $C_{28}H_{33}N_3O_3$, *M* = 459.2516, Orthorhombic, $P2_12_12_1$, *a* = 10.4419(4) Å, *b* = 15.1318(6) Å, *c* = 15.7265(8) Å, *V* = 2484.86(19) Å^3, *Z* = 4, *Dc* = 1.228 Mg m^{-3}, μ = 0.08 mm^{-1}, 8839 reflections, 308 parameters, *R* = 0.1207, *Rw* = 0.1846 for all data, $[\alpha]_D$ = +116.6 (c = 3.4, $CHCl_3$).

(*R*)-**3**: R_f = 0.27 (hexanes:EtOAc = 3:1), ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.32-7.30 (m, 2H), 7.26-7.05 (m, 3H), 6.78-6.70 (m, 2H), 6.70-6.41 (m, 2H), 5.88-5.65 (m, 1H), 5.19-5.01 (m, 2H), 4.13-4.02 (m, 1H), 3.95-3.78 (m, 1H), 3.75 (s, 3H), 2.71-2.60 (m, 1H), 2.59-2.42 (m, 2H), 2.29-2.18 (m, 1H), 2.18-2.09 (m, 1H), 2.01-1.94 (m, 2H), 1.35-1.285 (m, 2H), 1.09 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 139.4, 138.5, 132.9, 128.5, 125.8, 122.8, 121.5, 118.9, 117.5, 114.9, 114.8, 58.8, 57.8, 55.7, 54.3, 46.1, 39.8, 37.4, 29.7, 28.1, 26.8, 20.3, 20.0; HRMS *m/z* 459.2527 (calcd for $C_{28}H_{33}N_3O_3$: 459.2516), $[\alpha]_D$ = -88.6 (c = 1.0, $CHCl_3$).

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8. The X-ray structure data of (*S*)-**3** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 639469.
9. The use of other allylation reagents such as allyltrimethoxysilane, allyltrimethylsilane and allyltrichlorosilane resulted in either trace amounts of products or no reaction under the optimum reaction conditions.