Diastereoselective Synthesis of 1,3-*syn*-Oxazines via a Tandem Hemiaminalization and Tsuji–Trost Reaction

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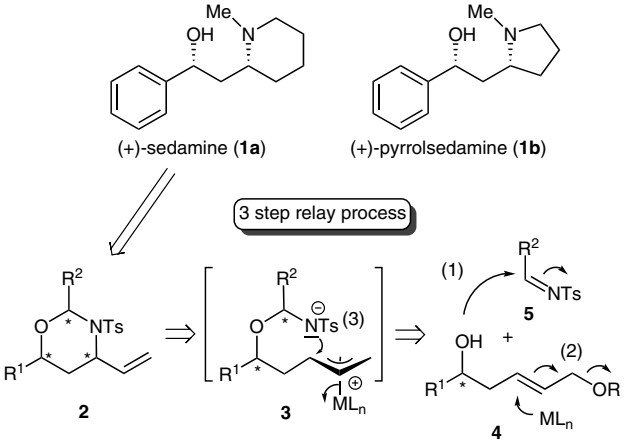
Received: 03.12.2012; Accept after revision: 31.01.2013

Abstract: A novel domino sequence for the rapid assembly of 1,3-*syn*-substituted oxazines is reported. Mechanistically, the one-pot procedure is based on a three-step sequential process involving a hemiaminalization and Tsuji–Trost reaction. The process generates up to two new stereogenic centers in a concise and convergent fashion from simple and readily available starting materials.

Key words: synthetic methodology, tandem reaction, catalysis, allylic substitution, oxazines

As exemplified by the potent alkaloids sedamine (**1a**) and pyrrolsedamine (**1b**, Scheme 1),[2] the 1,3-hydroxylamine functionality presents a prevalent structural feature in a wide variety of biologically active natural products and bioactive agents,[3] which renders the development of efficient synthetic procedures for their assembly an important research goal from the perspective of medicinal chemistry and drug discovery. Consequently, a wide variety of methods have been reported to access this structural feature.[4] Inspired by present targets in our group in combination with certain limitations of these existing methods, in particular with respect to convergence and conciseness, we desired a more direct and convergent procedure, relying on a readily available chiral alcohol functionality. Herein, we report a novel process for the concise construction of protected 1,3-*syn*-amino alcohols from readily available starting materials, based on a relay sequence involving a tandem hemiaminalization and an intramolecular allylic substitution reaction.

Inspired by previous sequential processes developed in our group,[5] our synthetic approach to access the protected 1,3-amino alcohol functionality was based on a three-step sequential process, involving a hemiaminalization[6] and subsequent allylic substitution. As shown in Scheme 1, homoallylic alcohol **4** would first add to a suitable imine (**5**). Secondly, a π-allyl complex **3** would be generated, which would be finally trapped in an intramolecular fashion by an allylic substitution reaction, generating the desired oxazine motif in a highly direct fashion. Along this process, two new stereogenic centers are formed, demonstrating a high increase in structural complexity from simple starting materials. A related sequence, as reported by the groups of Campagne and Robiette,[4l] relies on the addition of homoallylic alcohols to tosyl isocyanate giving the corresponding cyclic carbamates. Using their approach the *trans* diastereomers may be obtained in useful yields, in contrast to the results discussed herein giving access to the *syn* diastereomers. The group of Hiemstra had reported the attack of an hemiaminal derived from a sulfonamide and a glyoxylate to a double bond activated by Pd(II) giving an allylic *N*,*O*-acetal.[7]



Scheme 1

To test our concept, readily available homoallylic alcohol **6**[8] was treated with various tosylated aldimines[9] in the presence of allylpalladium(II) chloride dimer [{Pd(allyl)Cl}$_2$], triphenylphosphine and LHMDS as base (1.5 equiv) in accordance with similar conditions previously developed in our group for related transformations (entries 1–6).[4]

Gratifyingly, as shown in Table 1, the reaction worked indeed within expectation in good diastereoselectivities albeit low yield under these conditions (Table 1, entry 3). During further optimization studies (entries 7–11) it was then found that the amount of base was crucial for the process. Considering that the *tert*-butoxide anion formed during the Tsuji–Trost process[10] may itself act as a base and may then deprotonate the starting alcohol, we evaluated whether the desired transformation could also be effectuated with only catalytic amount of base (entries 7–11). Furthermore, based on the excellent selectivities obtained

SYNLETT 2013, 24, 0625–0629
Advanced online publication: 18.02.2013
DOI: 10.1055/s-0032-1318300; Art ID: ST-2012-B1033-L

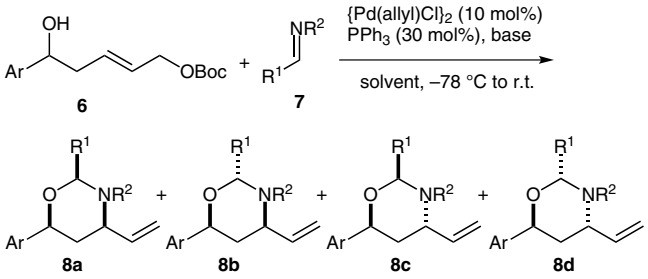
with acetaldimine (entry 3), a variety of aldimines were evaluated. It was found that the overall results of *N*-nosyl-protected phenyl aldimine were not improved (entry 7). Furthermore, no reaction occurred by utilizing *N*-Boc-protected phenyl aldimine (entry 8). Improved yields were observed by using *N*-tosyl-protected acetaldimine, however at the expense of diastereoselectivity (entries 9 and 11).

As shown in Table 2, this reaction was then further evaluated with different catalysts and ligands. Low degrees of conversion could also be observed in the complete absence of base, suggesting that the alcohol itself might be nucleophilic enough to initiate this sequential process.[12] Best yields were obtained with KHMDS as a base, toluene as solvent while a similar result was observed with tetrahydrofuran as solvent. In contrast to related cyclizations previously studied in our group,[5b] only a minor influence of the solvent on the stereochemical outcome of the reaction was observed. In a parallel fashion a variety of different palladium sources and ligands were also evaluated (entries 9–14); however, the overall efficiency of this process could not be further increased. The best reagent combination (entry 5) involved 30 mol% of triphenylphosphine as ligand and 10 mol% load of $\{Pd(allyl)Cl\}_2$ as catalyst dissolved in toluene adding the base (KHMDS, 10 mol%) at –78 °C and 15 minutes after addition warming the reaction mixture to room temperature.[13,14]

As shown in Figure 1, this protocol was readily applicable for the synthesis of diverse 1,3-oxazines with good selectivities considering the stereochemical complexity of the process. As compared to aliphatic substrates better stereoselectivities were obtained with electron-rich aromatic homoallylic substrates and were up to 10.1:1.0:2.7:2.8 (viz. **12**) which confirms the preparative utility of the process. The 1,3-*syn* diastereomer was preferentially obtained.

As demonstrated in Scheme 2 for the conversion of **11**, the aminal tether can be readily cleaved with activated magnesium powder,[5b] to deliver the *N*-benzyl-protected 1,3-amino alcohol **19**, demonstrating the usefulness of our approach for the synthesis of 1,3-*syn*-amino alcohols. Interestingly, this transformation led to an increased diastereomeric purity, possibly by a kinetic effect with the *syn* isomer reacting faster.

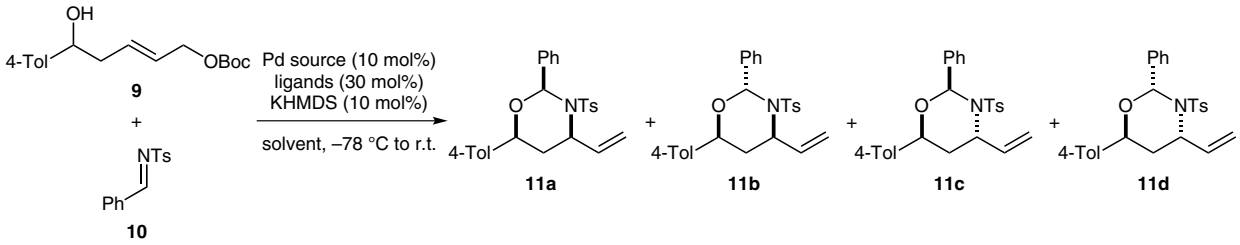
Table 1 Tandem Hemiaminalization–Tsuji–Trost Reaction[11]



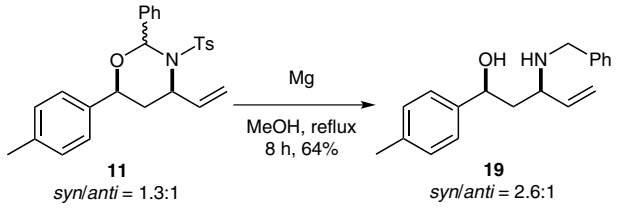
Entry	Ar	R^1	R^2	Base	Solvent	Yield (%)	dr (**a**/**b**/**c**/**d**)
1	Ph	Et	Ts	*t*-BuOK[a]	THF	15	–
2	Ph	2-$MeOC_6H_4$	Ns	LHMDS[a]	THF	9	–
3	4-Tol	Me	Ts	LHMDS[a]	THF	8	17.8:3.6:1.0:–[f]
4	4-Tol	Et	Ts	LHMDS[a]	THF	10	9.2:1.0: 2.1:–[f]
5	4-Tol	Ph	Ts	LHMDS[a]	THF	16[b]	1.0:1.5:4.8:0.3
6	4-Tol	*i*-Pr	Ts	LHMDS[a]	THF	n.r.	–
7	4-$MeOC_6H_4$	Ph	Ns	KHMDS[c]	toluene	39	2.6:1.4:2.4:1.0
8	4-$MeOC_6H_4$	Ph	Boc	KHMDS[c]	toluene	n.r.	–
9	Ph	Me	Ts	KHMDS[c]	toluene	64	4.9:1.4:1.0:5.4
10	4-$MeOC_6H_4$	Me	Ts	–[d]	THF	13	–[d]
11	4-$MeOC_6H_4$	Me	Ts	LHMDS[e]	THF	41	5.0:1.0:1.0:6.3

[a] The amount of base used was 1.5 equiv.
[b] One of two fractions in which the mixtures of isomers were partially separated by chromatography.
[c] The amount of base used was 10 mol%.
[d] No base was used.
[e] $Pd_2dba_3{\cdot}CHCl_3/P(i\text{-}PrO)_3$ was used as catalyst.
[f] Diastereomer **d** could not be detected by NMR of the crude product.

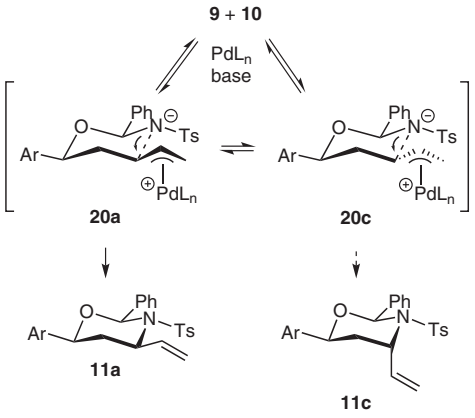
Table 2 Optimization of Reaction Conditions[11]



Entry	Pd catalyst/ligand	Base, solvent	Yield (%)	dr (**11a**/**11b**/**11c**/**11d**)
1	$\{Pd(allyl)Cl\}_2/PPh_3$	NaH, THF	n.r.	–
2	$\{Pd(allyl)Cl\}_2/PPh_3$	LiHMDS, THF	31	2.8:1.0:1.6:1.5
3	$\{Pd(allyl)Cl\}_2/PPh_3$	KHMDS, THF	60	3.9:1.0:2.0:1.5
4	$\{Pd(allyl)Cl\}_2/PPh_3$	KHMDS, CH_2Cl_2	29	1.2:1.0:1.1:1.3
5	**$\{Pd(allyl)Cl\}_2/PPh_3$**	**KHMDS, toluene**	**67**	**3.9:1.0:2.7:1.5**
6	$\{Pd(allyl)Cl\}_2/PPh_3$	DBU, toluene	59	2.5:1.0:3.0:1.2
7	$\{Pd(allyl)Cl\}_2/PPh_3$	Cs_2CO_3, toluene	31	3.9:1.0:2.3:2.6
8	$\{Pd(allyl)Cl\}_2/PPh_3$	KOtBu, toluene	35	3.5:1.0:2.6:2.0
9	$\{Pd(dppf)Cl\}_2$/dppf	KHMDS, toluene	12	1.1:1.0:1.6:0.6
10	$[Pd_2(dba)_3]\cdot CHCl_3/PPh_3$	KHMDS, toluene	48	2.7:1.0:1.8:0.1
11	$Pd(PPh_3)_4$/–	KHMDS, toluene	39	0.9:1.0:1.1:0.2
12	$\{Pd(allyl)Cl\}_2$/dppe	KHMDS, toluene	38	0.7:1.0:2.0:–
13	$\{Pd(allyl)Cl\}_2/PCy_3$	KHMDS, toluene	n.r.	–
14	$\{Pd(allyl)Cl\}_2/P(i\text{-}PrO)_3$	KHMDS, toluene	46	0.9:1.0:2.0:0.6



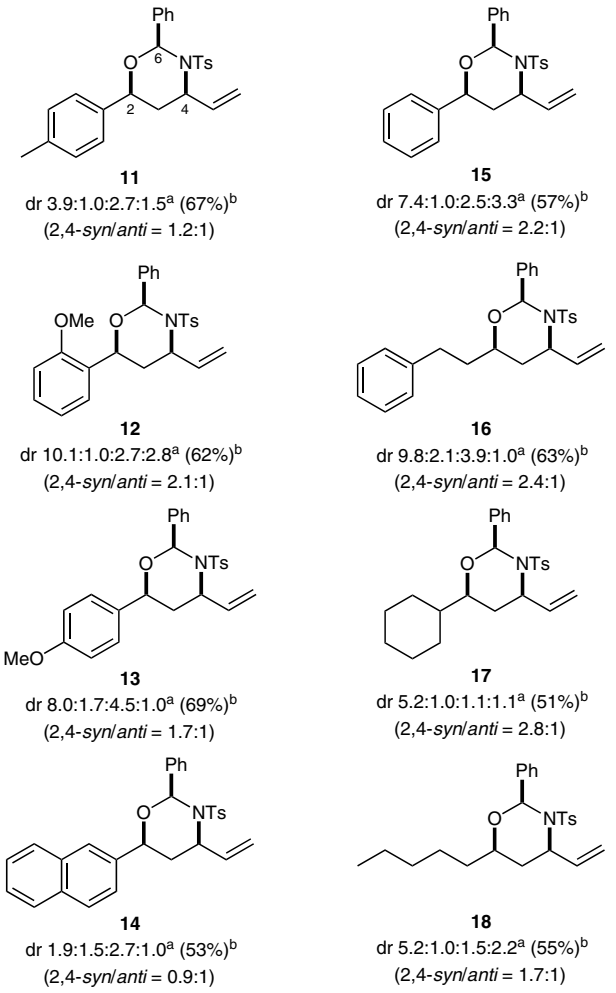
Scheme 2



Scheme 3

In accordance with related cyclizations,[5] the observed stereoselectivity may arise from a Zimmerman–Traxler-type transition state (**20a**, Scheme 3) giving **11a** with all substituents in equatorial positions, in agreement with the observed stereochemical outcome. Alternatively, attack from the opposite side of the π-allyl system via **20c** may lead to the less favored isomer **11c** with two of the three substituents residing in equatorial positions.[15]

In summary, we have devised a novel method for the stereoselective synthesis of 1,3-*syn*-oxazines. Mechanistically, the one-pot procedure is based on a tandem hemiaminalization with Tsuji–Trost reaction and it enables a rapid and highly convergent access to these heterocycles from very simple and readily available starting materials. 1,3-*syn* Diastereomers are obtained in good yields and selectivities, considering the stereochemical complexity of the process. The diastereomeric induction is purely based on substrate-control, which adds to the effectiveness of the process. These results may find useful applications in natural product synthesis or scaffold preparation in medicinal chemistry.



[a] dr for (6-*epi*)-, (4-*epi*)- and (4-*epi*, 6-*epi*)-isomer given
[b] combined yield

Figure 1

Acknowledgment

Generous financial support by the Deutsche Forschungsgemeinschaft (SFB 623 'Molekulare Katalysatoren: Struktur und Funktionsdesign') and the Chinese Scholarship Council (CSC, scholarship to B.T.) is gratefully acknowledged. Furthermore, we thank Andreas J. Schneider for HPLC support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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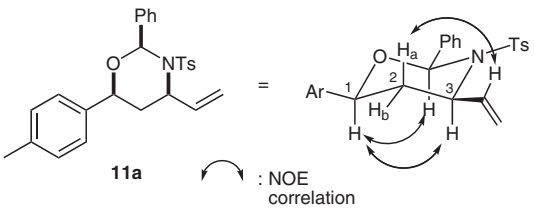
(11) In all cases, stereochemical assignment was based on NMR methods. Scheme 4 shows an example.



Scheme 4

(12) A yield of 56% was obtained in the absence of base for the analogous reaction described in entry 5 (Table 2).

(13) **Experimental Procedure**: Under an argon atmosphere, imine **10** (62.2 mg, 0.24 mmol), allylpalladium(II) chloride dimer (7.3 mg, 10 mol%) and triphenylphosphine (15.8 mg, 30 mol%) were added to a well-dried Schlenk flask. Then, a solution of the respective carbonate (0.2 mmol) in anhyd toluene (0.33 M, 0.61 mL) was added to the flask and stirred until all solids were dissolved. After cooling to –78 °C, the potassium bis(trimethylsilyl)amide solution (0.5 M in toluene) was added dropwise (40 μL, 10 mol%). After 15 min the reaction mixture was warmed to r.t. and stirred at this temperature until complete conversion. After addition of a sat. aq solution of NH_4Cl (2 mL), the mixture was extracted with EtOAc (3 ×), washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel with EtOAc–hexane (1:16) as eluent to afford the oxazines with the indicated yields and selectivities.

(14) All new compounds had spectroscopic data in support of the assigned structures. **Oxazine 11a**: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 8.5 Hz, 1 H) 7.63 (d, *J* = 8.2 Hz, 1 H), 7.58 (d, *J* = 8.2 Hz, 1 H), 7.29–7.42 (m, 5 H), 7.12–7.19 (m, 2 H), 7.07 (d, *J* = 7.9 Hz, 1 H), 7.00 (d, *J* = 7.9 Hz, 1 H), 6.75 (s, 1 H), 5.78 (ddd, *J* = 17.3, 10.4, 7.7 Hz, 1 H), 5.02 (d, *J* = 17.3 Hz, 1 H), 4.96 (d, *J* = 10.3 Hz, 1 H), 4.40 (ddd, *J* = 8.5, 8.2, 7.7 Hz, 1 H), 3.86 (dd, *J* = 10.2, 4.7 Hz, 1 H), 2.50 (s, 3 H), 2.35 (s, 3 H), 1.93 (ddd, *J* = 13.7, 10.2, 8.2 Hz, 1 H), 1.54 (ddd, *J* = 13.7, 8.5, 4.7 Hz, 1 H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 143.93, 141.52, 139.12, 137.74, 137.48, 137.36, 129.78, 129.19, 129.14, 128.27, 128.02, 127.82, 127.63, 127.29, 126.81, 126.17, 125.71, 115.73, 83.83, 73.15, 56.10, 33.62, 21.58, 21.08. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{28}NO_3S$: 434.17844; found: 434.17839. **Oxazine 12a**: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.91–7.96 (m, 4 H), 7.71 (d, *J* = 7.7 Hz, 2 H), 7.50 (d, *J* = 7.7 Hz, 2 H), 7.32–7.40 (m, 5 H), 6.73 (s, 1 H), 5.78 (ddd, *J* = 17.3, 10.4, 6.6 Hz, 1 H), 5.02 (d, *J* = 17.3 Hz, 1 H), 4.94 (d, *J* = 10.4 Hz, 1 H), 4.50 (ddd, *J* = 8.2, 8.0, 6.6 Hz, 1 H), 4.34 (dd, *J* = 11.5, 2.2 Hz, 1 H), 3.71 (s, 3 H), 2.48 (s, 3 H), 2.07 (ddd, *J* = 13.7, 8.0, 2.2 Hz, 1 H), 1.82 (ddd, *J* = 13.7, 11.5, 8.0 Hz, 1 H). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 155.85, 143.35, 141.45, 139.34, 131.19, 129.72, 129.06, 128.57, 128.00, 127.90, 127.65, 126.89, 126.29, 120.62, 115.46, 110.29, 84.36, 68.03, 55.78, 55.09, 33.19, 21.54. HRMS (ESI): *m*/*z* $[M + K]^+$ calcd for $C_{26}H_{27}NO_4SK$: 488.12924; found: 488.12948.

(15) For a more detailed mechanistic discussion of a related cyclization, see ref. 4d.