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A one-pot stereoselective synthesis of *trans*-1-aryl-2-aminotetralins from 2-arylethyl styrenes

Saumen Hajra *, Biswajit Maji, Debarshi Sinha, Sukanta Bar

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

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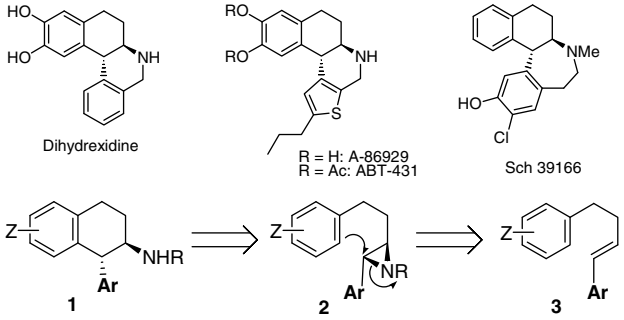
Abstract

An efficient stereoselective synthesis of *trans*-1-aryl-2-aminotetralins has been achieved via $Cu(OTf)_2$ catalyzed one-pot aziridination and regioselective intramolecular arylation of in situ generated aziridines from 2-arylethyl styrenes and $PhINSO_2(4\text{-}NO_2C_6H_4)$ [PhINNs]. Reaction of a mixture of *E*/*Z*-styrenes (⩽85:15) provided trans-N-protected-1-aryl-2-aminotetralins with high diastereoselectivity (dr > 95:5), which are important synthons for many artificial pharmaceuticals.

1-Aryl-2-aminotetralin **1** is the key precursor to many biologically active compounds, in particular, artificial pharmaceuticals such as dihydrexidine, A-86929 and Sch39166.[1–3] Concise stereoselective synthesis of *trans*-tetralin **1** is, therefore, highly desirable in organic and medicinal chemistry. A straightforward synthetic approach towards **1** is the stereoselective intramolecular arylation of tethered aziridines (Scheme 1). In contrast to the extensive study on aziridine ring opening with a number of nucleophiles,[4] intramolecular electrophilic arylation with tethered aziridines has not been explored.[5] Our efforts[6] towards electrophilic arylation with alkenes via reactive intermediates led us to investigate this chemistry. Herein, we report our preliminary results on the stereoselective one-pot synthesis of *trans*-1-aryl-2-aminotetralins via $Cu(OTf)_2$ catalyzed intramolecular arylation of in situ generated aziridines.

Cu(I) and Cu(II) are excellent catalysts for the aziridination of alkenes with $PhINSO_2Ar$.[4] Thus, we began our studies on the reactions of 2-phenylethyl styrene **3a** with $PhINSO_2(4\text{-}MeC_6H_4)$ [PhINTs] and $PhINSO_2(4\text{-}NO_2C_6H_4)$ [PhINNs] in the presence of commonly available Cu-catalysts (Table 1). The CuCl, $CuCl_2$ and



Scheme 1.

$Cu(OAc)_2$ catalyzed reactions with PhINTs as a nitrenoid source produced traces of products after 12 h (entries 2, 4 and 6). In the case of PhINNs, the CuCl catalyzed reaction afforded exclusively aziridine **2a**, no cyclized product **1a** was obtained even after a prolonged reaction time (entry 3). With $CuCl_2$ and $Cu(OAc)_2$ as catalysts, mixtures of **1a** and **2a** were obtained (entries 5 and 7). The $Cu(OTf)_2$ catalyzed reactions both with PhINTs and with PhINNs provided directly **1a** in 40% and 56% yields, respectively (entries 8 and 9). The catalytic reaction of **3a** with PhINNs to produce **1a** was found to be better in CH_2Cl_2(56%) compared to dichloroethane (51%), benzene (41%) and acetonitrile (45%), and there was no reaction in THF, DMF

* Corresponding author. Tel.: +91 3222 283340; fax: +91 3222 255303.
E-mail address: shajra@chem.iitkgp.ernet.in (S. Hajra).

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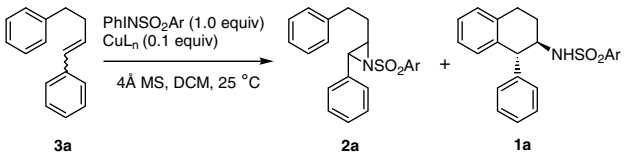
Table 1
Screening of copper catalysts for the intramolecular arylation and in situ generation of aziridine of **3a**[a]



Entry	CuL_n	Nitrogen source	*t* (h)	Yield[b] **2a** (%)	Yield[b] **1a** (%)
1	None	PhINTs/PhINNs	12	NR	
2	CuCl	PhINTs	12	Traces	—
3	**CuCl**	**PhINNs**	**12**	**51**	—
4	$CuCl_2$	PhINTs	12	Traces	Traces
5	$CuCl_2$	PhINNs	12	20	30
6	$Cu(OAc)_2$	PhINTs	12	Traces	Traces
7	$Cu(OAc)_2$	PhINNs	12	18	12
8	**$Cu(OTf)_2$**	**PhINTs**	**10**	—	**40**
9	**$Cu(OTf)_2$**	**PhINNs**	**8**	—	**56**

[a] A suspended solution of **3a** (5 equiv), $PhINSO_2Ar$ (1.0 equiv), 4 Å MS (0.2 g/mmol of **3a**) and CuL_n(0.1 equiv) in CH_2Cl_2 was stirred at 25 °C.
[b] Isolated yield after column chromatography.

and MeOH. Traces of product **1a** were observed in chloroform. Thus, when a suspended solution of **3a** (*E*/*Z* 75:25; 5.0 equiv), PhINNs (1.0 equiv) and 4 Å MS in CH_2Cl_2 was treated with $Cu(OTf)_2$ (0.1 equiv) at 25 °C, *trans*-1-phenyl-2-aminotetralin **1a** was obtained in 8 h with >95:5 diastereoselectivity in 56% yield. ^1H NMR spectral analysis of the crude reaction mixture revealed the formation of traces (6%) of the *cis*-aziridine *cis*-**2a**, but no cis-cyclized product *cis*-**1a** was observed. It appears that both the *cis*-styrene and the *cis*-aziridine might be less reactive than the corresponding trans-isomer. To examine this pure *cis*-alkene *cis*-**3a** reacted with PhINNs under the same reaction conditions. After 3 h, the formation of *cis*-aziridine *cis*-**2a** was detected by ^1H NMR, but no cyclized product (Scheme 2) and 42% of *cis*-**2a** was isolated after 8 h. When the same reaction was continued with an additional amount of $Cu(OTf)_2$ (0.5 equiv), a non-separable mixture of unidentified compounds was formed. It is worth mentioning that when pure **2a,** obtained from the reaction in Table 1, entry 3, was treated with $Cu(OTf)_2$ (0.1 equiv), the cyclized product **1a** was produced in 2 h in quantitative yield.

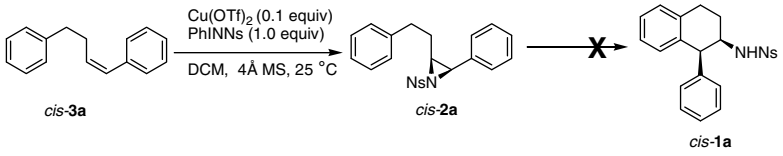
Next, we investigated the scope of the catalytic method for the synthesis of N-protected 1-aryl-2-aminotetralins (Table 2).[7,8] Substrate **3a** smoothly underwent $Cu(OTf)_2$ catalyzed intramolecular arylation of the tethered in situ generated aziridine with PhINNs and afforded product **1a** in 56% yield (entry 1). The formation of aziridine intermediate **2a** was detected by ^1H NMR and was isolated as a

Table 2
$Cu(OTf)_2$ catalyzed one-pot synthesis of N-protected 1-aryl-2-aminotetralins[a]

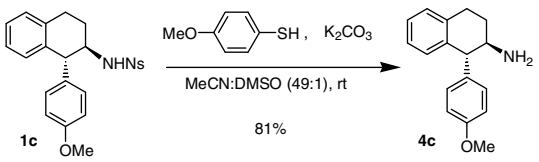
Entry	Substrate (*E*:*Z*)[b]	*t* (h)	Product	Yield[c] (%)
1	**3a** (75:25)	8	**1a**	56
2	**3b** (63:37)	6	**1b**	61
3	**3c** (75:25)	3	**1c**	80
4	**3d** (75:25)	4	**1d**	68
5	**3e** (67:33)	5	**1e**	78
6[d]	**3f** (85:15)	2.5	**1f**	58

[a] A suspended solution of substrate **3** (5 equiv), PhINNs (1.0 equiv), 4 Å MS (0.2 g/mmol of **3**) and $Cu(OTf)_2$(0.1 equiv) in CH_2Cl_2 was stirred at 25 °C.
[b] Synthesis of styrenes **3a–f** is described in the Supplementary data.
[c] Isolated yield after column chromatography.
[d] Reaction was carried out at 0 °C.

minor product when the reaction was stopped after 4 h. The reactivity of**3b** was comparable with **3a** and afforded the desired product **3b** in 61% yield under the same reaction conditions (entry 2). Substrates **3c–e** having electron-rich aromatic rings at either end of the alkene chain underwent fast reactions and gave good yields of **1c–e** (entries 3–5). The more electron-rich substrate **3f** gave a clean reaction at 0 °C affording a moderate yield of **1f** (entry 6). Unlike **3a**, no intermediate aziridines **2c–f** and *cis*-**2c–f** were



Scheme 2.



Scheme 3.

detected for the reaction of substrates **3c–f**. It should be noted that the reaction was judged to be complete as soon as all the nitrenoid reagents had dissolved in the reaction medium. Allowing the reactions to proceed further resulted in the formation of more by-products. In all the cases, PhINNs was used as a limiting reagent (1.0 equiv) with an excess of styrene **3** (5 equiv) to ensure complete consumption of aziridine reagent. If substrate **3** was used as the limiting reagent, that is, 1.0 equiv of **3** and 1.2 equiv of PhINNs, the yield was reduced to almost half and also the generation of undesired by-products increased.

Deprotection of the amide[9] of **1** followed by Pictet–Spengler cyclization would provide the important hexahydrobenzo[*a*]phenanthridine. As an example, compound **1c** was treated with 4-methoxythiophenol and K_2CO_3 in CH_3CN/DMSO (49:1) at rt, to produce *trans*-1-(4-methoxyphenyl)-2-aminotetralin **4c**[10] in 81% yield in 3 h (Scheme 3).

In summary, we have developed an efficient one-pot protocol for the stereoselective synthesis of *trans*-1-aryl-2-aminotetralins from 2-arylethyl styrenes via Cu(II) catalyzed aziridination and subsequent regio- and stereoselective intramolecular arylation of the in situ generated aziridine. The combination of $Cu(OTf)_2$ as a catalyst and PhINNs as a nitrene source was found to be superior for the reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.056.

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7. *General procedure* : To a well-stirred suspended solution of PhINNs (0.1 g, 0.25 mmol), 2-phenylethyl styrene **3a** (0.26 g, 1.23 mmol) and 4 Å MS (0.25 g) in dry DCM (4 ml), $Cu(OTf)_2$ (0.009 g, 0.025 mmol) was added and the heterogeneous reaction mixture was stirred at room temperature for 8 h under an argon atmosphere. On completion, the reaction was quenched with water and extracted with Et_2O (3×10 ml). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude mass was subjected to purification by flash column chromatography using pet-ether (60–80)/EtOAc to obtain pure 4-nitro-*N*-(1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-benzenesulfonamide **1a** (0.056 g, 56% yield) as a white solid.
8. All the compounds listed in Table 2 were characterized by ^1H and ^{13}C NMR spectroscopy. The following are the representative spectral data of **1a** and **1c**.4-Nitro-*N*-(1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-benzenesulfonamide (**1a**): White solid. Mp 171–173 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, $J = 8.8$ Hz, 2H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.20–7.04 (m, 5H), 7.00 (m, 1H), 6.83 (d, $J = 7.0$ Hz, 2H), 6.61 (d, $J = 7.6$ Hz, 1H), 4.76 (d, $J = 7.2$ Hz, 1H), 3.85 (d, $J = 8.4$ Hz, 1H), 3.68–3.57 (m, 1H), 3.15–2.98 (m, 1H), 2.90 (m, 1H), 2.45–2.30 (m, 1H), 1.91–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.5, 145.7, 142.7, 136.2, 135.4, 130.4, 129.0 (2C), 128.6 (2C), 127.8 (2C), 127.0, 126.7 (2C), 126.3, 124.1 (2C), 57.3, 52.0, 28.9, 27.1. HRMS (EI) calcd for $C_{23}H_{20}N_2O_4S$, 431.1041 *m/z* $(M+Na)^+$; found, 431.1042 *m/z*.*N*-[1-(4-Methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitro-benzenesulfonamide (**1c**): White solid. Mp 120–122 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, $J = 8.8$ Hz, 2H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.13 (m, 2H), 7.00 (m, 1H), 6.73 (d, $J = 8.4$ Hz, 2H), 6.62 (d,$J = 7.6$ Hz, 1H), 6.58 (d, $J = 8.4$ Hz, 2H), 4.75 (d, $J = 7.2$ Hz, 1H), 3.77 (d, $J = 8.4$ Hz, 1H), 3.73 (s, 3H), 3.65–3.48 (m, 1H), 3.12–2.95 (m, 1H), 2.92 (m, 1H), 2.46–2.35 (m, 1H), 1.90–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6, 149.5, 145.8, 136.7, 135.3, 134.5, 130.3, 129.8 (2C), 128.5, 127.9 (2C), 126.2, 125.9, 123.9 (2C), 113.8 (2C), 57.7, 55.0, 51.3, 29.4, 22.6. HRMS (EI) calcd for $C_{23}H_{22}N_2O_5S$, 461.1147 *m/z* $(M+Na)^+$; found, 461.1147*m/z*.
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10. Compound **4c** was characterized by ^1H and ^{13}C NMR spectroscopy.1-(4-Methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl amine (**4c**): Gummy liquid. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.18–7.00 (m, 5H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.61 (d, $J = 8.0$ Hz, 1H), 3.87 (d, $J = 8.0$ Hz, 1H), 3.74 (s, 3H), 3.30 (m, 1H), 3.00–2.85 (m, 2H), 2.03 (m, 1H), 1.88 (s, 2H), 1.71 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.4, 138.3, 136.1, 135.8, 130.6 (2C), 130.1, 128.8, 126.3, 126.2, 114.3 (2C), 55.4, 53.8, 51.5, 28.0, 27.2. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.72; H, 7.68; N, 5.56.