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Oxazolines as chiral building blocks for imidazolium salts and N-heterocyclic carbene ligands†

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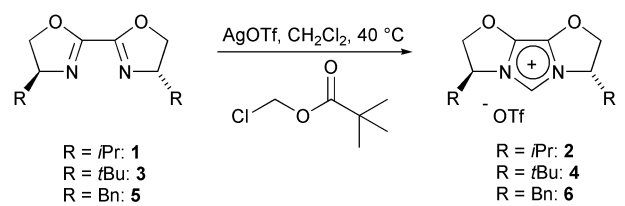
Enantiomerically pure imidazolium triflates can be readily prepared from bioxazolines and oxazolineimines; deprotonation of imidazolium triflate 2 gives a chiral N-heterocyclic carbene that can act as a ligand in a catalytically active palladium complex.

Transition metal complexes of N-heterocyclic carbenes (NHC) are an important class of compounds for coordination chemistry and catalysis.[1] The strong σ-donor properties of NHC's combined with poor π-acceptor ability result in metal complexes with high chemical and thermal stability together with good catalytic activity. Successful application of these complexes in asymmetric catalysis is evolving,[2] but electronic and steric variations of NHC's will be necessary for further progress in this field.

Oxazolines are powerful structural elements, which have been incorporated in many chiral ligands successfully used in asymmetric catalysis.[3] However, despite their obvious benefits they have not as yet been used as building blocks to form other functional groups in chiral ligands. We reasoned that incorporation of oxazolines into imidazolium salts would lead to valuable rigid ligand architectures. We began our investigations with readily available (*S*)-valinol derived bioxazoline **1**.[4] In analogy to procedures for the transformation of glyoxal derived diimines into imidazolium salts,[5] we treated **1** with chloromethyl ethyl ether in THF at 40 °C. Instead of imidazolium salt formation the attack of chloride anions led to opening of the oxazoline rings. The additional use of stoichiometric amounts of silver triflate in CH_2Cl_2 was found to give the desired **2**, together with other products in a complex mixture. Screening of other silver salts with different solvents at various temperatures did not improve the results. Fortunately, using silver triflate in combination with chloromethyl pivalate instead of chloromethyl ethyl ether led to the clean conversion of **1** to imidazolium triflate **2** in an isolated yield of 80% (Scheme 1).‡ The structure of **2** was unequivocally determined by an X-ray crystallographic analysis.[6] Following the same procedure (*S*)-*tert*-leucinol derived bioxazoline **3** gave imidazolium triflate **4** in 75% yield. To the best of our knowledge, these compounds represent the first 4,5-dialkoxy-substituted 1,3-disubstituted imidazolium salts. Furthermore, this new method works equally well for milligram and multigram quantities. In contrast to many other imidazolium salts[7] the resulting triflate salts are readily soluble in CH_2Cl_2 or THF and can be purified by column chromatography followed by crystallisation.

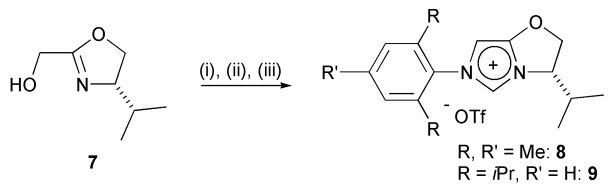


Scheme 1

† Electronic supplementary information (ESI) available: spectroscopic data for **10** and **12**. See http://www.rsc.org/suppdata/cc/b2/b208045a/

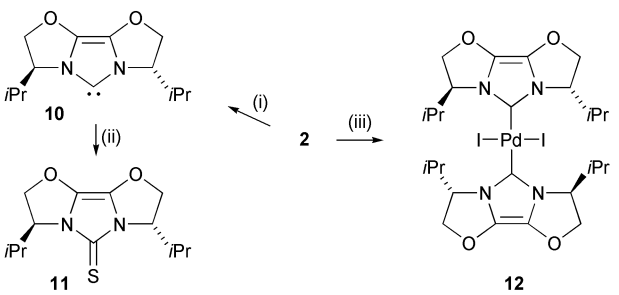
Presumably AgCl and trifluoromethylsulfonyloxymethyl pivalate are formed under the reaction conditions. The latter enables the smooth alkylation of the acid and nucleophile sensitive oxazolines and subsequent cyclisation to give the obtained imidazolium salts in high yields. However, treatment of benzyl substituted bioxazoline **5** under the described reaction conditions did not give any product **6** due to the formation of a stable silver complex of **5**. In this case stirring of AgOTf and chloromethyl pivalate in CH_2Cl_2 for 1 h, followed by filtration and subsequent addition of the filtrate to **5** led to the formation of the desired imidazolium salt **6**. Difficulties in the purification of **6** are responsible for the low yield of 36%.

To expand the scope of this new synthetic method we synthesised unsymmetrical oxazolineimines from readily available alcohol **7**[8] by oxidation with MnO_2 followed by imine formation with the corresponding aniline derivatives. We were pleased to find that submission of these oxazolineimines to the standard cyclisation conditions led to the smooth formation of the imidazolium triflates **8** and **9** in 80 and 83% yield, respectively (Scheme 2).[9]



Scheme 2 *Reagents and conditions*: (i) MnO_2, NEt_3, EtOH; (ii) aniline derivative, toluene, reflux; (iii) AgOTf, chloromethyl pivalate, CH_2Cl_2, 40 °C.

With these imidazolium salts in hand we were prompted to investigate their transformation into NHC's and metal complexes thereof. Imidazolium triflate **2** was readily deprotonated with 10 mol% KO*t*Bu and a stoichiometric amount of KH to give N-heterocyclic carbene **10** (Scheme 3). This carbene is reasonably stable in THF at r.t. and was characterized by its NMR data. In a carbene-typical reaction[10] addition of sulfur led to the formation of imidazole-2(3*H*)-thione **11**. Palladium complex **12** was best prepared by deprotonation of the imidazolium salt **2** in the presence of the palladium precursor with a stoichiometric amount of KO*t*Bu. Purification by flash



Scheme 3 *Reagents and conditions*: (i) KH, KO*t*Bu, THF; (ii) S_8, 59% (two steps); (iii) $Pd(OAc)_2$, KO*t*Bu, NaI, THF, 87%.

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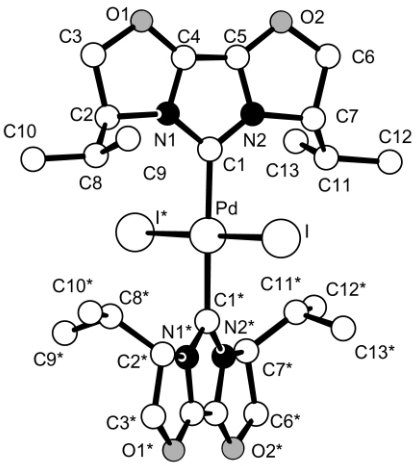


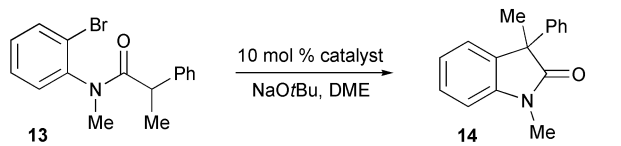
Fig. 1 Structure of **12**. Selected distances (Å) and angles (°): Pd–C1 2.035(3), Pd–I 2.6139(5), C8···C8* 3.838(11), C11···C11* 3.819(12); C1–Pd–C1* 179.0(3), mean plane (C1–C6, N1, N2, O1, O2, Pd)/mean plane (C1*–C6*, N1*, N2*, O1*, O2*, Pd) 50(1).

chromatography yielded the air-stable complex **12** in 87% yield. Unlike related palladium complexes,[11] **12** was formed solely as the *trans* isomer. The structure was validated by an X-ray structure analysis (Fig. 1).[6] In the crystal the molecule adopts a conformation in which the two imidazolylidene ligands are twisted relative to one another, resulting in short H···H contacts (2.06, 2.15 Å)[12] between the methyne H atoms of isopropyl groups on adjacent ligands, presumably caused by steric interaction between the chirally positioned isopropyl groups and the iodide ligands.

Lee and Hartwig recently reported on the enantioselective α-arylation of amides, giving oxindole **14** in an isolated yield of 74% with 57% ee using 5 mol% of catalyst.[13] We chose **13** as substrate to test the imidazolium triflates **2**, **4** and **6** (Table 1). Using imidazolium salt **2** as a NHC precursor and a Pd(0) or Pd(2) source in a 1:1 ratio gave a very good yield of oxindole **14** with an ee of around 30% (entries 1 and 2). Complex **12** could also be used as a catalyst precursor; however, higher temperature and a longer reaction time were needed (entry 3). Interestingly, 40% of complex **12** were recovered after completion of the reaction. Slightly better results were obtained with the *t*Bu-substituted imidazolium triflate **4**. With $Pd_2(dba)_3$ the reaction was run at r.t. and gave the product **14** in a very good yield and with 43% ee (entry 4). At a slightly higher temperature the reaction could also be brought to completion using only 1 mol % of the catalyst (entry 6).

In conclusion, we report a new straightforward method to transform bioxazolines and oxazolineimines into enantiomerically pure imidazolium salts, which opens up the possibility of synthesising a new class of N-heterocyclic carbenes for asymmetric catalysis.

Table 1 Enantioselective α-arylation of amide **13**



Entry	Catalyst	*T*/°C	Time/h	Yield[a] (%)	% Ee[b]
1	**2** + $Pd_2(dba)_3$	50	5	85	28 (+)
2	**2** + $Pd(OAc)_2$	50	5	92	32 (+)
3	**12**	90	20	95	30 (+)
4	**4** + $Pd_2(dba)_3$	20	14	95	43 (+)
5	**4** + $Pd(OAc)_2$	50	14	90	35 (+)
6[c]	**4** + $Pd_2(dba)_3$	50	14	97	37 (+)
7	**6** + $Pd_2(dba)_3$	50	16	90	11 (+)

[a] Isolated yield. [b] Determined by HPLC with Chiralcel OD–H. [c] 1 mol% catalyst.

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Notes and references

‡ *General imidazolium triflate formation*: to a mixture of bioxazoline **1** (5.0 g, 22.2 mmol) and AgOTf (6.8 g, 26.6 mmol) were added CH_2Cl_2 (75 mL) and then chloromethyl pivalate (4.6 mL, 31.2 mmol). The tube was sealed and stirred in the dark at 40 °C for 24 h. After the solution was cooled to r.t. the mixture was filtered, the solvent evaporated *in vacuo* and the resulting oil was chromatographed on silica gel (4 × 10 cm, CH_2Cl_2–MeOH 20:1). Subsequent crystallisation from a solvent mixture comprising THF (30 mL), toluene (150 mL) and pentane (50 mL) gave 6.85 g (80%) of imidazolium triflate **2** as colorless crystals.

R_f = 0.37 ($CHCl_3$–MeOH 93:7); $[\alpha]^{20}_D$ = 55.0 (*c* 1.0, CH_2Cl_2); IR (KBr): 3110, 2970, 1731, 1532, 1481, 1285, 1261, 1154, 1032, 966, 917, 882, 826, 755, 638; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H, NCHN), 5.07 (dd, *J* 7.9, 9.0 Hz, 2H, CH_2), 4.98–4.93 (m, 2H, C*H*CH_2), 4.83 (dd, *J* 4.1, 9.0 Hz, 2H, CH_2), 2.33 (m, 2H, C*H*CH_3), 1.03 (d, *J* 6.9 Hz, 6H, CH_3), 0.99 (d, *J* 6.9 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6 (NCO), 120.6 (q, *J* 320 Hz, CF_3), 116.3 (NCHN), 79.1 (CH_2), 63.9 (*C*HCH_2), 31.1 (*C*HCH_3), 17.6 (CH_3), 16.7 (CH_3); ^{19}F NMR (300 MHz, $CDCl_3$): δ −78.7 (CF_3); MS (EI), *m*/*z* (%) 386 (0.4) [M^+], 237 (100), 169 (5), 69 (7); MS (ESI+): *m*/*z* (%) 237 (100). HRMS (EI): calc. for $C_{13}H_{21}N_2O_2$ (cation): 237.1603, found 237.1605. Anal. Calc. for $C_{14}H_{21}F_3N_2O_5S$: C, 43.52; H, 5.48. Found C, 43.44; H, 5.55%.

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