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Concise Synthesis of the Antidepressive Drug Candidate GSK1360707 by a Highly Enantioselective Gold-Catalyzed Enyne Cycloisomerization Reaction

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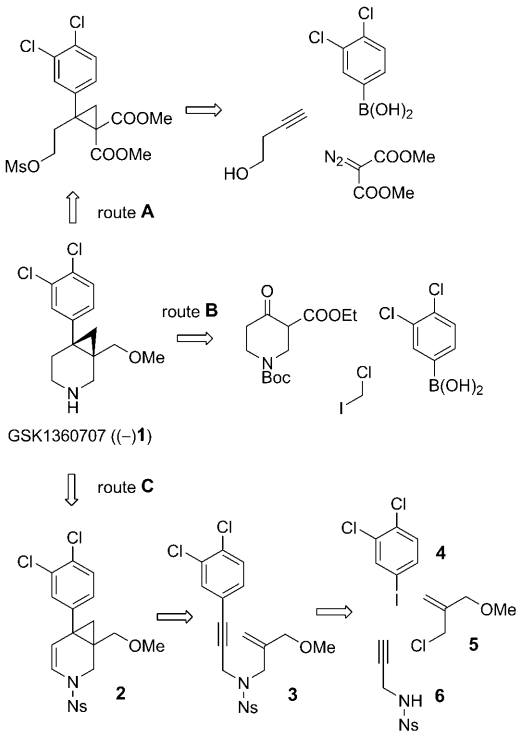
Depression is a serious chronic illness that exacts a significant toll on health and productivity in the entire western world. Although various lines of treatment are established, medication with antidepressive agents is most common, which usually act by increasing the levels of the excitatory neurotransmitters serotonin, noradrenaline, and dopamine.[1] This can be achieved by down-regulating either the metabolization of these key aminergic messengers or their reuptake from the synaptic cleft by the presynaptic neurons. Whereas most of the approved drugs interfere with the serotonin reuptake, more advanced medication attempts to interfere with two or preferably even all three of these crucial neurotransmitters simultaneously to better address the anhedonic symptoms of depression and/or shorten the time to onset of clinical efficiency.[1] GSK1360707 represents a particularly promising "triple-reuptake inhibitor", which was recently progressed into clinical trials because it had shown promising bioavailability and pharmacokinetics, together with a well-balanced activity profile in animal experiments.[2]

So far, three different syntheses of GSK1360707 and salts thereof were disclosed in patents and/or the open literature (Scheme 1). The lengthy original approach (route **A**, 13 steps total, 11 linear steps, 5% overall yield) was deemed inappropriate for scale up as it required the use of diazomalonate and comprised a low-yielding resolution as the final step.[3] A much improved second generation synthesis follows a significantly shorter sequence (Scheme 1, route **B**, 5 steps, 21% overall yield), which could be performed on a pilot plant scale to produce multikilogram amounts of the drug candidate.[4] However, high cost of goods, not least for the advanced starting material, a fairly low atom economy, the troublesome production of polychlorinated biphenyl derivatives as byproducts in the necessary Suzuki reaction, and the need for a chromatographic separation of the enantiomers on a chiral stationary phase in the penultimate step are still far from ideal.[4] Therefore, yet another synthesis was pursued, which was based on the formation of the tricyclic skeleton by a noble-metal-catalyzed enyne cycloisomerization (route **C**).[5] In adaptation of chemistry originally described by our group,[6] the development team managed to form the key intermediate **2** from substrate **3** in excellent yield with the aid of $PtCl_2$ (3.5 mol%) as the catalyst (7 steps, 45(58)% overall yield).[7] $PtCl_2$ could also be replaced by gold-based catalysts, but attempts to perform the rearrangement asymmetrically with enantiopure LAu^+ templates were plagued by low enantiomeric excesses (*ee*), despite the considerable number of well-established chiral ligands (**L**) that were tested. The best results were obtained with a combination of $AuCl{\cdot}SMe_2$ (10 mol%), (*R*)-tol-BINAP (5 mol%) and $AgBF_4$ (10 mol%), which afforded compound **2** in 59% *ee*.[5] Prompted by this recent disclosure,[5] we now present our approach to the triple-reuptake inhibitor GSK1360707, which is not only even shorter and significantly more efficient, but also provides the desired product in excellent optical purity. It attests to the power



Scheme 1. Published syntheses of the triple-reuptake inhibitor GSK1360707 ((−)-**1**), all of which require a resolution step; Ms = methanesulfonyl; Boc = *tert*-butyloxycarbonyl; Ns = 2-nitrophenylsulfonyl.

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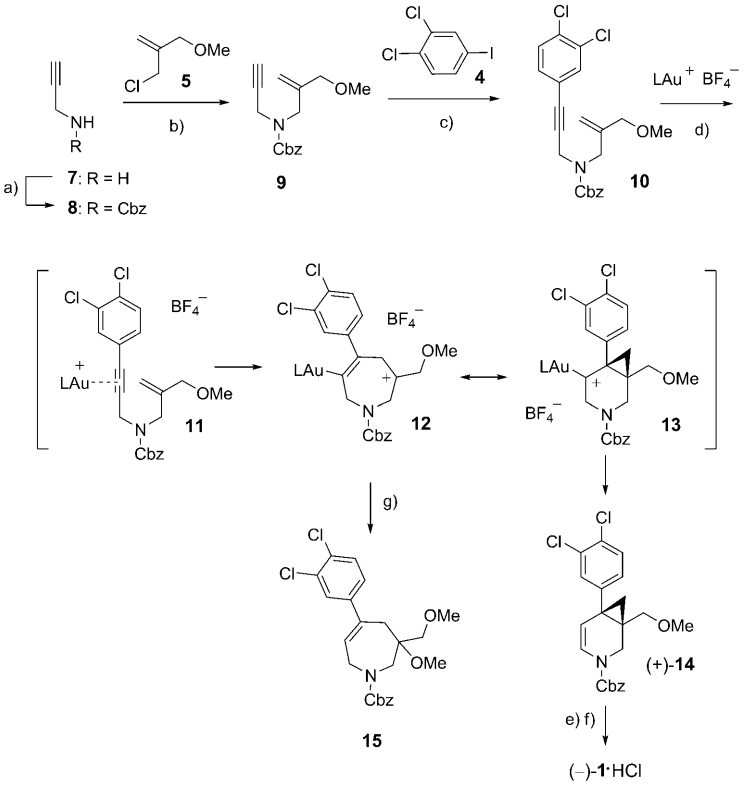
and the flexibility of the ligand-design concept for asymmetric gold catalysis recently disclosed by this laboratory.[8]

Our approach capitalized on the simple notion that replacement of the *N*-nosyl (Ns) group in **2**[5] by a benzyloxycarbonyl (Cbz) moiety might streamline the end part of the synthesis. Whereas compound **2** had to be transformed into the target in a stepwise manner using Et_3SiH and trifluoroacetic acid to reduce the enamide followed by cleavage of the nosyl group with thioglycolic acid in basic medium,[5] we envisaged a straightforward catalytic hydrogenation/hydrogenolysis step for the release of the final product in a single operation. To this end, propargyl amine was acylated with CbzCl, followed by N-alkylation of the resulting compound **8** with the substituted allyl chloride **5** (Scheme 2).[9] As expected, the subsequent Sonogashira coupling with 1,2-dichloro-4-iodobenzene **4** under standard conditions also proceeded smoothly[10] to give enyne **10** as the required cyclization precursor in excellent yield.

Asymmetric gold catalysis is particularly exigent because Au^I strongly favors linear dicoordination.[11,12] This handicap forces the substrate to approach the active center *trans* to the chosen chiral ligand **L**, which itself can be attached to the metal center only by single-point binding and hence is able to rotate freely about the **L**–Au bond. In a previous communication we showed that these challenges can be met by crafting chiral pockets with an effective threefold symmetry.[8] The environment in the resulting binding site is degenerate upon rotation of **L** and should therefore translate into good enantioselectivity. In fact, readily accessible phosphoramidite ligands,[13] preferably those comprising 2,3-dimethoxy-1,1,4,4-tetraarylbutane-1,4-diol entities as TADDOL-related units[14] with an acyclic backbone, were shown to form such C_3-symmetric ligand spheres about a Au^I center and turned out to impart excellent levels of asymmetric induction onto [2+2] and [4+2] cycloadditions of ene–allene substrates.[8]

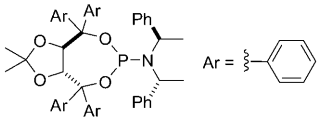
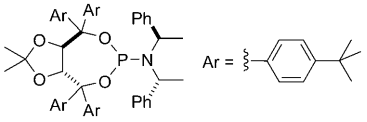
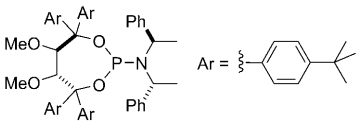
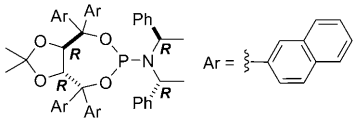
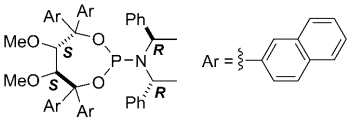
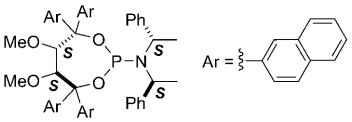
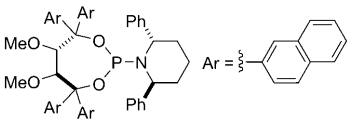
At first, however, applications of these ligands to the cycloisomerization of enyne **10** met with limited success. Under the standard conditions of our earlier studies, product **14** was obtained with only moderate *ee* values independent of the chosen phosphoramidite.[15] Even **L3**, which had been the most effective ligand in the ene–allene series,[8] gave compound **14** with no more than 44% *ee* (entry 3). Gratifyingly though, it was found that changing the solvent from the previously used CH_2Cl_2 to toluene resulted in a dramatic improvement, with **14** now being formed with 90% *ee*. This favorable outcome stands in marked contrast to the report by the Glaxo chemical development group, which did not find any significant effects on the outcome of their reaction when changing the solvent, the counterion, or the temperature.[5] In our case, however, the positive effect of toluene turned out to be general as can be seen from the data compiled in Table 1. Even more surprising is the observation that the switch from CH_2Cl_2 to toluene even inverted the sense of induction when the parent TADDOL ligand **L1** was used.[16]



Scheme 2. Enantioselective synthesis of GSK1360707: a) CbzCl, $NaHCO_3$, EtOH/H_2O (1:1), 0°C→RT, quant; b) Compound **5**, NaH, THF/DMF (1:1), 0°C→RT, 91%; c) Compound **4**, $[(Ph_3P)_2PdCl_2]$ (2.5 mol%), CuI (5 mol%), Et_3N, DMF, 95%; d) [LAuCl] cat., $AgBF_4$ cat., see Table 1; e) Pd black (2.5 mol%), H_2 (1 atm), Na_2CO_3, EtOAc/MeOH (1:1), 91%; f) HCl in ether (1 M), Et_2O, quant; g) $[(PhO)_3PAuCl]$ (5.5 mol%), $AgBF_4$ (5 mol%), MeOH/CH_2Cl_2 (1:1), 49% (95% based on recovered starting material). Cbz = benzyloxycarbonyl.

Previous crystallographic information had suggested that the C_3-symmetric chiral pocket grafted by a phosphoramidite with a TADDOL backbone carrying unsubstituted phenyl rings (Ar = Ph) would not reach over the big Au^I cation by much. To extend the binding site and ensure better chiral recognition, *tert*-butyl groups had been attached to the 4-position of these decisive substituents as shown in ligands **L2** and **L3**.[8] An obvious alternative is the annulation of a second ring; this design is reduced to practice in ligands **L4**–**L7** carrying 2-naphthyl rather than (4-*tert*-butyl)phenyl moieties. All of them performed exceedingly

Table 1. Enantioselective cycloisomerization of enyne **10** to product (+)-**14** (indicated by "+") or its enantiomer (indicated by "−") using complexes of the general type [**L**AuCl] as precatalysts.[a]

Entry	Ligand	(**L**)	**L**·AuCl [mol %]	*ee* [%] CH_2Cl_2	*ee* [%] toluene
1		**L1**	5.5	+48	−26
2		**L2**	5.5	−23	
3		**L3**	5.5	−44	−90
4		**L4**	5.5	−48	−84
5		**L5**	5.5		+90
6		**L6**	5.5		+93
7		**L6**	2.75		+95[b,c,d]
8		**L7**	5.5	+53	+94
9		**L7**	5.5		+95[b]

[a] Unless indicated otherwise, all reactions were performed at ambient temperature using $AgBF_4$ (5 mol %) as co-catalyst; the conversion was quantitative in all cases investigated. [b] At 0 °C. [c] With only 2.5 mol % of $AgBF_4$ as co-catalyst. [d] Product **14** was isolated in 88 % yield on a 1 mmol scale.

well in the current application, with **L6** and **L7** both giving the desired product **14** in up to 95 % *ee*. In this context it should be noted, that the level of induction is only marginally improved upon lowering the temperature (Table 1, compare entries 6 to 7 and 8 to 9), whereas the reaction rate is decreased. It is also noteworthy that replacement of $AgBF_4$ by non-hygroscopic $AgNTf_2$ shut down the reaction (<5 % conversion after 24 h, as determined by NMR analysis).

In line with the rationale previously outlined,[8] the data compiled in Table 1 shows that all TADDOL's with an acyclic backbone performed significantly better than their traditional analogues carrying an acetal moiety. This observation is true for all cases in which direct comparisons can be made and is independent of the chosen solvent (Table 1, compare entries 2 to 3 and 4 to 6).

Another striking result pertains to the fact that the absolute configuration of **14** is determined solely by the stereochemistry of the TADDOL unit of the ligand, whereas the configuration of the amine part is not decisive.[17] Specifically, both antipodes of 1-phenylethylamine afforded the same enantiomer of **14** with appreciable levels of induction (Table 1, compare entries 4 to 5 and 5 to 6), indicating that the match/mismatch between the TADDOL and amine plays a minor role. (*S,S*)-2,6-Diphenylpiperidine[18] gave essentially the same outcome as its acyclic congener bis(*S*)-1-phenylethylamine (compare entries 6 to 8 and 7 to 9). For practical reasons, however, ligand **L6** was preferred because bis(*S*)-1-phenylethylamine is commercially available. With 2.75 mol % of the readily prepared, air stable and hence very practical complex **L6**·AuCl in combination with 2.5 mol % of $AgBF_4$ in toluene at 0 °C,[19] we were able to obtain the desired cycloisomerization product (+)-**14** in 88 % yield with a well reproducible *ee* value of 95 %.

When the reaction was performed in MeOH as co-solvent, the rather unstable tertiary ether **15** was obtained as the only product. We tentatively interpret this result as an indication for the "non-classical" character of the reactive intermediate primarily formed in noble-metal-catalyzed enyne cycloisomerization reactions.[6,20] For gold in particular, it has been computed that the putative cyclopropyl carbenes are actually highly distorted and largely resemble the canonical form of a gold-stabilized homoallyl cation;[21] this particular resonance extreme **12** is then intercepted by the external nucleophile at its tertiary cation site, at which the charge density is most stabilized.[22] It is interesting to note, however, that **12** has an achiral scaffold, whereas the bond formation that converts **12** into **13** is enantio-determining. This may help rationalize the high enantioselectivity observed with our system, because induction occurs only after the substrate has been covalently linked to the gold template and hence deeply immersed into the chiral pocket.[23]

Finally, the choice of the *N*-Cbz group paid dividends; stirring a solution of enamide **14** in a mixed solvent system (EtOAc/MeOH, 1:1) under an atmosphere of hydrogen in the presence of palladium black and Na_2CO_3, ensured the deprotection and saturation of the double bond in a single operation.[24] Under these conditions, no signs of cyclopro-

pane opening or reductive cleavage of the chlorine substituents were noticed, and (−)-**1** was obtained in a spectroscopically and analytically pure form after simple extraction; as expected, the *ee* value was fully preserved (as determined by HPLC analysis). However, since the free amine is a liquid, it was preferable to convert the crude material into an appropriate salt such as the crystalline hydrochloride (−)-**1**·HCl;[25] recrystallization then allows trace amounts of metal impurities to be removed, which are strictly regulated in any drug candidate. Overall, the route to the triple-reuptake inhibitor GSK1360707 presented herein requires no more than 5 operations, provides this valuable antidepressive agent with 95% optical purity in an overall yield of no less than 69%, and hence clearly surpasses all known routes in terms of efficiency and stereoselectivity. We are currently further extending the scope of the chiral gold catalysts described herein and will report our results in due course.

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Keywords: asymmetric catalysis · cycloisomerization · drug design · gold · phosphoramidites

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[24] Inspection of the NMR spectra shows that the Cbz group is quickly cleaved; the hydrogenation of the resulting imine required stirring overnight at ambient temperature.

[25] Various other salts of **1** are also known in the literature, see ref. [3]–[5].

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