Asymmetric Catalysis

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Enantioselective Gold Catalysis: Opportunities Provided by Monodentate Phosphoramidite Ligands with an Acyclic TADDOL Backbone**

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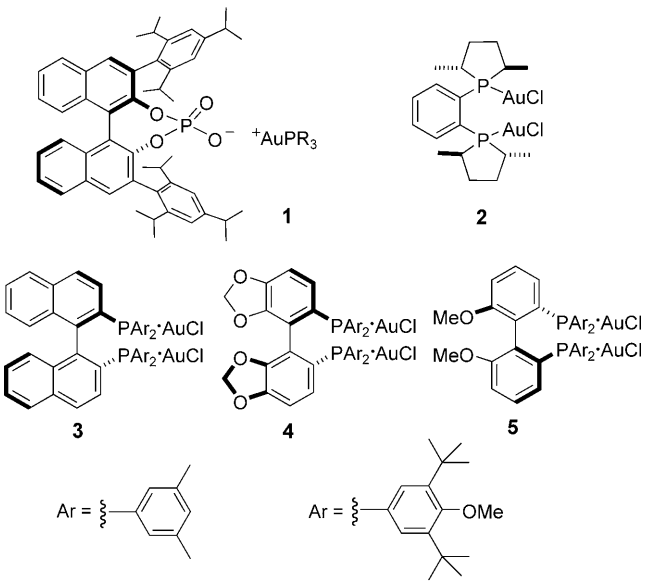
Electrophilic activation of π systems using platinum and gold complexes is an active frontier of contemporary catalysis research.[1,2] These exceedingly practical carbophilic Lewis acids allow readily available substrates to be converted into diverse carbocyclic or heterocyclic scaffolds with a significant increase in molecular complexity.[3] Although inherently apt for asymmetric synthesis, the development of effective chiral gold catalysts poses considerable challenges,[4] not least because of the strong preference of Au^I for linear dicoordination. This geometry precludes the chelation of a bidentate chiral ligand to a single metal center, which arguably constitutes the most successful strategy in asymmetric catalysis to date.[5] Moreover, the reacting substrate is forced to approach the reactive gold center *trans* to the ancillary ligand (L*), which further hinders the transfer of chiral information.

Two different approaches have been reported to overcome these problems.[4,6] First, the use of chiral counterions as an escort for a cationic gold template has been successful in certain cases (see complex **1**).[7] Second, dinuclear diphosphine complexes, such as **2**–**5**, have proven effective, even though careful optimization is necessary to match substrate and catalyst.[8] However, the bis(phosphine) ligands in **2**–**5** are elaborate, difficult to modify, and can be more expensive than the noble metal they bind to; therefore, alternative design principles are highly desirable. Herein, we report our approach, which exploits a previously unrecognized opportunity in TADDOL chemistry[9] for the development of powerful phosphoramidite gold catalysts.[10]

Early attempts to use the BINOL-derived phosphoramidite containing complex [**6**·AuCl] in asymmetric gold-catalysis essentially met with failure (<2% *ee*),[11] and only recently has this class of ligands been re-utilized. Mascareñas et al. showed that the highly crowded variant [**7**·AuCl] successfully effected the [4+2] cycloadditions of allene–dienes in good to excellent enantioselectivity.[12] In parallel studies, our research group found that complex [**8**·AuCl],[13,14] which also contains bulky substituents at the 3,3′-positions of the BINOL core, is useful for the enantioselective cyclopropanation of styrene derivatives (Scheme 1).[8a]



Although this result merits further investigation, a catalyst screen gave another promising hit. Complex **12a**,[15] which contains a much simpler TADDOL-derived phosphoramidite, furnished cycloadduct **14**[16] with 84% *ee* (Table 1). Variation of the ligand constituents showed that: 1) bis(1-phenylethyl)amine **15** performed best amongst all amine components investigated,[14] and 2) (*R*,*R*)-**15** and (*R*,*R*)-TADDOL form a matched pair.[14] Moreover, the arene moiety exerted a striking influence on the outcome. Whereas **12a** (Ar = Ph) and **12b** (Ar = C_6H_4OMe) gave similar results, phenyl groups containing electron-withdrawing substituents at the *meta* or *para* positions afforded higher reaction rates but significantly lower enantioselectivities (Table 1, entries 3–5). A through-bond effect seems unlikely to explain these striking differences in selectivity and reactivity because the ^{31}P NMR shifts of the corresponding gold complexes do not change much within the entire series (Table 1); rather, a through-space interaction between the arenes and the electron deficient Au^+ center is more plausible.[17] In this case, a higher electron density at the aromatic periphery should tighten the chiral pocket, but also lower the electrophilicity, and hence decrease the activity of the gold complex after ionization with $AgBF_4$.

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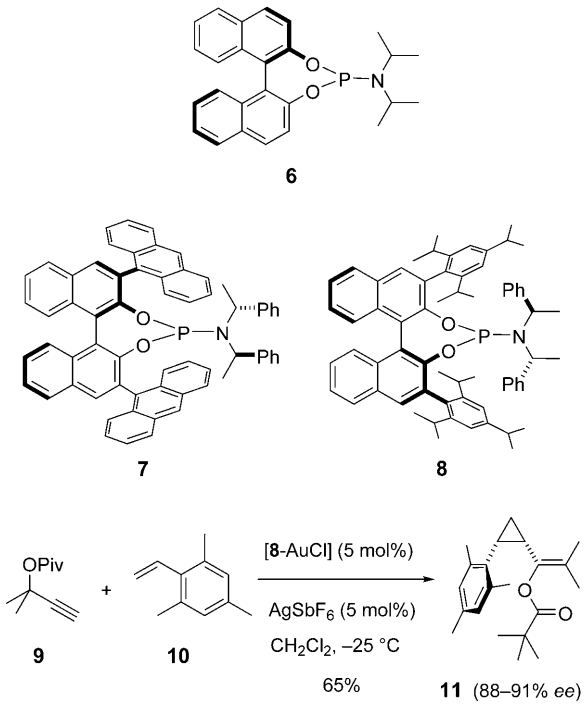
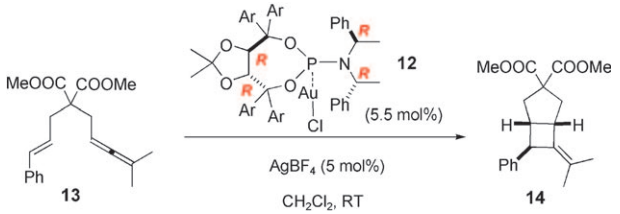


Scheme 1. BINOL-derived phosphoramidites for asymmetric gold catalysis. Piv = pivaloyl.

Table 1: Influence of remote substituents on the arene part of the TADDOL ligand **12** on the enantioselectivity and reaction rate of gold-catalyzed [2+2] cycloaddition reactions.[18]



Entry	Ar		*t* [h]	Yield [%]	*ee* [%]	δ_P (ppm, C_6D_6)
1		**12a**	2	93	84	113.5
2	4-OMe	**12b**	16	90	86	112.5
3	4-Cl	**12c**	1	95	75	113.6
4	4-F	**12d**	1	84	39	113.8
5	3,5-CF_3	**12e**	1	88	20	117.3
6	3-*t*Bu, 4-OMe, 5-*t*Bu	**12f**	>16	71	63	112.7

The structure of gold complex **12a** in the solid state supports this view. Two phenyl rings of the TADDOL and one phenyl substituent of the amine form a cone-shaped binding pocket of approximate C_3 symmetry (red; Figure 1). All three

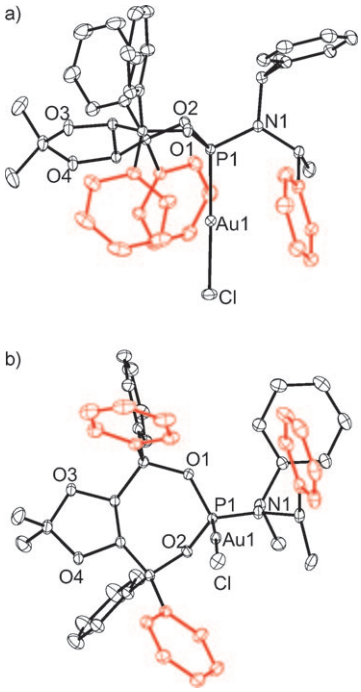
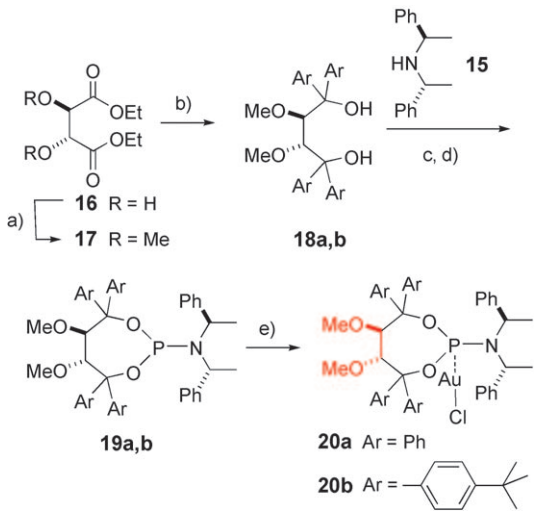


Figure 1. Structure of complex **12a** in the solid state in two orientations: a) perpendicular to the P–Au–Cl axis and b) along the P–Au–Cl axis. These structures show the binding pocket around the gold center, which is formed from three phenyl groups of the ligand (red). Ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity.[14]

arenes orientate one edge toward the AuCl unit, even though the contacts are not uniformly close (the distances from the gold center to the C_{ipso} atoms are 3.230(1), 3.284(1), and 3.971(1) Å). One of the phenyl rings of the TADDOL part is slightly bent away from the metal, which presumably undermines the enantioselective binding event of the substrate to the gold center. The crystal structure of the analogous complex **12b**, which contains *para*-methoxyphenyl rather than unsubstituted phenyl rings on the TADDOL, shows very similar structural features.[14] Importantly, however, the corresponding Au–C_{ipso} distances in **12b** are shortened to 3.196(1), 3.292(1), and 3.766(1) Å, thus lending credence to the notion that a more electron-rich periphery in the ligand maintains closer interactions with the metal,[17] and thereby possibly improves the asymmetric induction at the expense of the reaction rate (Table 1, entries 1 and 2).[14]

We envisaged that this apparently important secondary interaction between the peripheral arenes and the metal would be reinforced if the third phenyl ring is moved closer to the metal. To this end, the isopropylidene acetal was removed from the TADDOL backbone and replaced with a dimethyl ether motif (Scheme 2). We expected that the seven-membered ring of the resulting phosphoramidite **19**, relieved from the constraints of annulation, would be sufficiently flexible, to bring the third arene ring into a truly axial orientation. To the best of our knowledge, TADDOL derivatives containing an acyclic skeleton have so far not been successfully used in asymmetric catalysis,[9,19] even though compounds **18a**,**b** and the derived phosphoramidites **19a**,**b** are readily accessi-



Scheme 2. Preparation of phosphoramidite gold complexes **20a,b** that have a TADDOL subunit with an acyclic backbone. a) NaH, dimethyl sulfate, Et_2O, 0°C→RT, quant. yield; b) ArMgBr (5 equiv), THF, 0°C→RT, 57% yield (Ar = Ph), 67% yield (Ar = tBuC$_6$H$_4$); c) PCl_3, Et_3N, toluene (0.02 M), 4 Å M.S., 0°C→60°C; d) **15**, nBuLi, THF, −78°C→RT, 58% yield (**19a**), 67% yield (**19b**); e) $NaAuCl_4 \cdot 2H_2O$, 2,2′-thiodiethanol, $CHCl_3/H_2O$ (1:5), 99% yield (**20a**), 95% yield (**20b**).

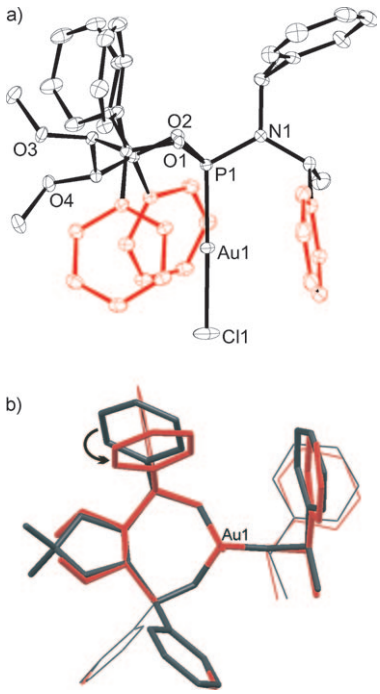
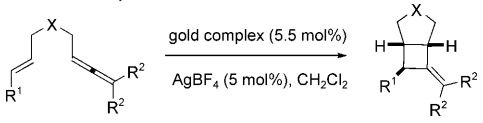


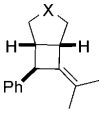
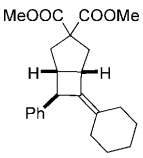
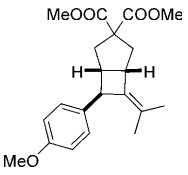
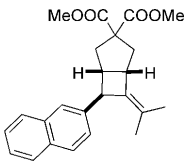
Figure 2. a) Structure of complex **20a** in the solid state.[14] b) Overlay of the crystal structures of complex **12a** (black) and **20a** (red) along the Cl–Au–P axis. This comparison shows that the acyclic TADDOL backbone in **20a** affords a tighter binding pocket about the gold atom by bringing the third phenyl ring into closer contact (see arrow). Ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity.

ble.[14,20] Like their annulated analogues **12**, the corresponding gold complexes **20a** (δ_P = 112.8 ppm) and **20b** (δ_P = 113.7 ppm) are air-stable and therefore convenient precatalysts. The structure of **20a** in the solid state (Figure 2) retains the favorable features of parent compound **12a**; however, its seven membered ring is slightly more puckered, bringing the third phenyl group into significantly closer contact with the gold center (the corresponding Au–C_{ipso} distance is shortened from 3.971(1) Å (**12a**) to 3.505(1) Å in **20a**); this tighter and more regular binding pocket crafts what appears to be an effective C_3-symmetric chiral environment.

Provided that the structure of **20** in the solid state is maintained in solution, this precatalyst should furnish higher enantioselectivities than the original catalyst **12a**. In fact, the *ee* value for the [2+2] cycloaddition product **14** was improved from 84% (**12a**) to 94% (**20a**), and ≥99% *ee* was obtained with complex **20b**, which contains *tert*-butyl substituents on the phenyl rings (Table 2).[21] This result clearly surpasses the selectivity obtained with the much more expensive and elaborate dinuclear SEGPHOS complex **4** (95% *ee*).[16] Gratifyingly, the outstanding level of selectivity was retained throughout the entire series; even the *N*-tosyl derivative **23** showed excellent optical purity (95% *ee*), although complex **4** furnished this product in only 54% *ee*.[16] Moreover, the novel

Table 2: [2+2] Cycloaddition reactions[a] catalyzed by different gold–phosphoramidite complexes.[18]

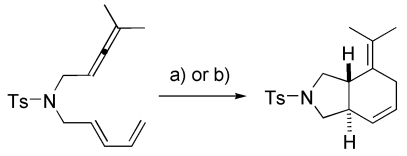


Product		Gold complex 12a	20a	20b	Yield [%][e]
	**14** X = C(COOMe)$_2$	84%	94%	≥99%	91
	21 X = C(COOBn)$_2$	82%	96%	≥99%	98
	22 X = C(COOtBu)$_2$	79%	95%	99%	94
	23 X = NTs	86%[b]	87%[b]	95%[b]	52[c]
	**24**	84%[b]	92%[b]	≥99%[b]	93
	**25**	87%	91%	99%[d]	94
	**26**	88%	92%	98%	87

[a] All reactions were performed at 0°C unless otherwise stated. [b] At room temperature. [c] 65% yield, based on recovered starting material. [d] According to HPLC, the product contains 6.7% of an unknown isomer. [e] Yield obtained using complex **20b**.

phosphoramidites with an acyclic backbone contained in catalyst **20** gave consistently better results than the standard isopropylidene analogue used in **12a** (Table 2).

Complex **20b** also performed well in the [4+2] cycloaddition of allene–diene **27** (Scheme 3), with comparable selectivity to [**7**·AuCl].[12a,c,22,23] Importantly, this [4+2] cycloaddition is mechanistically distinct from the [2+2] cycloadditions that are summarized in Table 2; strong evidence has been reported suggesting that the former cycloaddition occurs in a concerted manner, whereas the latter proceed by a



27 **28**

Scheme 3. Comparison of two gold phosphoramidite complexes in the asymmetric [4+2] cycloaddition of allene–diene **27**: a) [**7**·AuCl] (2 mol%), $AgSbF_6$ (2 mol%), CH_2Cl_2, −15 °C, 92% yield, 92% *ee* (Ref. [12a]), or b) **20b** (5.5 mol%), $AgBF_4$ (5 mol%), CH_2Cl_2, 0 °C, 90% yield, 91% *ee*.

stepwise, cationic mechanism.[24] Therefore, we conclude that the new phosphoramidite complexes described herein represent cheap, practical, stable, and highly enantioselective alternatives to the established ligands in the field of asymmetric gold catalysis. Our rational approach was made possible by the first productive use of a TADDOL derivative with an acyclic backbone in asymmetric catalysis. We intend to develop this design concept further, investigate the preparative scope of the new complexes and their congeners in more detail, and establish a better understanding of the underlying mechanisms.[25]

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[1] For selected reviews, see: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; d) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; e) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817–7831; f) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; g) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; h) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; i) A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 4118–4136; *Angew. Chem. Int. Ed.* **2007**, *46*, 4042–4059.

[2] For our initial studies in this area, see: a) A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.

[3] A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

[4] For short reviews, see: a) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181; b) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391.

[5] *Comprehensive Asymmetric Catalysis, Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[6] The first reported asymmetric gold-catalyzed process was an isocyanide aldol reaction, which is mechanistically different from the π-acid catalysis reported herein, see: Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

[7] a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; b) K. Aikawa, M. Kojima, K. Mikami, *Angew. Chem.* **2009**, *121*, 6189–6193; *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.

[8] a) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003; b) C. González-Arellano, A. Corma, M. Iglesias, F. Sánchez, *Chem. Commun.* **2005**, 3451–3453; c) M. A. Tarselli, A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 6790–6793; *Angew. Chem. Int. Ed.* **2007**, *46*, 6670–6673; d) C. Liu, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 1935–1938; e) Z. Zhang, R. A. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287–289; *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285; f) R. L. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453; g) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *129*, 14148–14149; h) A. D. Melhado, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12638–12639; i) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057; j) C.-M. Chao, M. R. Vitale, P. Y. Toullec, J.-P. Genêt, V. Michelet, *Chem. Eur. J.* **2009**, *15*, 1319–1323; k) F. Kleinbeck, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 9178–9179.

[9] For a comprehensive review, see: D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96–142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138.

[10] For leading reviews on phosphoramidites and related ligands, see: a) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267–1277; b) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353; c) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592–2626; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556–2588.

[11] M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300.

[12] a) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030; b) for a racemic synthesis, see: P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349; c) while this manuscript was under review, another closely related 3,3′-disubstituted BINOL-derived phosphoramidite as well as a C_3-symmetric phosphite ligand were reported; see: A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 200–203.

[13] S. Flügge, Dissertation, TU Dortmund, **2009**.

[14] For crystallographic data, further screening results and the full experimental data, see the Supporting Information. CCDC 754596 [**8**·AuCl], 754597 (**12a**), 754598 (**12b**), and 754599 (**20a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

[15] a) This and related TADDOL-derived phosphoramidites are known in the literature, but their syntheses are fairly low yielding; see: A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, F. Mazé, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011–4027. For an improved synthesis, see the Supporting Information; b) for a recent application of related phosphoramidites in a cycloaddition

reaction, see: R. T. Yu, R. Keller Friedman, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13250 – 13251.

[16] M. R. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402 – 12403. The absolute configuration of the product is still to be determined. We refrain from presenting a transition state model for the enantioselective step before this crucial point has been unambiguously clarified.

[17] For interactions between Au^+ ions and arene rings, see: a) F.-B. Xu, Q.-S. Li, L.-Z. Wu, X.-B. Leng, Z.-C. Li, X.-S. Zeng, Y. L. Chow, Z.-Z. Zhang, *Organometallics* **2003**, *22*, 633 – 640; b) Q.-S. Li, C.-Q. Wan, R.-Y. Zou, F.-B. Xu, H.-B. Song, X.-J. Wan, Z.-Z. Zhang, *Inorg. Chem.* **2006**, *45*, 1888 – 1890; c) E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5581 – 5585; *Angew. Chem. Int. Ed.* **2006**, *45*, 5455 – 5459; d) V. Lavallo, G. D. Frey, S. Kousar, B. Donnadieu, G. Bertrand, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13569 – 13573.

[18] It is important to avoid an excess of $AgBF_4$ as this may result in the decomposition of the chiral cationic catalyst and promote racemic background reactions. Therefore, 5.5 mol% of [LAuCl] but only 5 mol% of $AgBF_4$ were used.

[19] a) The application of a TADDOL ligand containing a bis-(acetate) backbone in a Baeyer–Villiger oxidation using a Sharpless-type reagent combination was unsuccessful; see: T. Kanger, K. Kriis, A. Paju, T. Pehk, M. Lopp, *Tetrahedron: Asymmetry* **1998**, *9*, 4475 – 4482; b) for studies on the host properties of such compounds, see: F. Toda, K. Tanaka, Z. Stein, I. Goldberg, *J. Chem. Soc. Perkin Trans. 2* **1993**, 2359 – 2361; c) F. Toda, K. Tanaka, *Tetrahedron Lett.* **1988**, *29*, 551 – 554.

[20] a) D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehring, W. Langer, C. Nüssler, H.-A. Oei, M. Schmidt, *Helv. Chim. Acta* **1977**, *60*, 301 – 325; b) O. De Lucchi, P. Maglioli, G. Delogu, G. Valle, *Synlett* **1991**, 841 – 844.

[21] For a recent example in which a TADDOL derivative, containing *tert*-butyl groups on its arene moieties, performs better than the parent phenyl analogue, see: M. R. Albicker, N. Cramer, *Angew. Chem.* **2009**, *121*, 9303 – 9306; *Angew. Chem. Int. Ed.* **2009**, *48*, 9139 – 9142.

[22] Complexes [**7**·AuCl] and **20b** both furnish the (+)-isomer, the absolute configuration of which was determined by Mascareñas et al., see Ref. [12a].

[23] For an alternative approach to gold-catalyzed [4+2] cycloaddition reactions, see: A. Fürstner, C. C. Stimson, *Angew. Chem.* **2007**, *119*, 9001 – 9005; *Angew. Chem. Int. Ed.* **2007**, *46*, 8845 – 8849, and references therein.

[24] D. Benitez, E. Tkatchouk, A. Z. Gonzalez, W. A. Goddard, F. D. Toste, *Org. Lett.* **2009**, *11*, 4798 – 4801.

[25] a) A. Fürstner, L. Morency, *Angew. Chem.* **2008**, *120*, 5108 – 5111; *Angew. Chem. Int. Ed.* **2008**, *47*, 5030 – 5033; b) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem.* **2009**, *121*, 2548 – 2551; *Angew. Chem. Int. Ed.* **2009**, *48*, 2510 – 2513.

