CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002606

Gold-Catalyzed Direct Activation of Allylic Alcohols in the Stereoselective Synthesis of Functionalized 2-Vinyl-Morpholines

Marco Bandini,* Magda Monari, Alessandro Romaniello, and Michele Tragni[a]

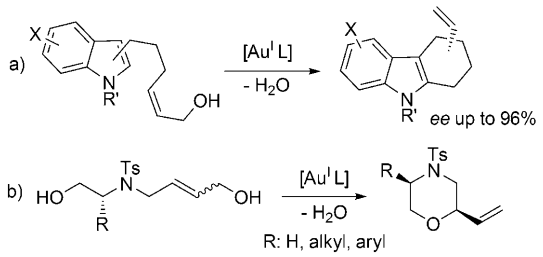
Dedicated to Professor Achille Umani-Ronchi for his life-long commitment to the advancement of organic synthesis

Gold catalysis has contributed remarkably to the development of organic synthesis over the last few years, opening access to a plethora of new chemical transformations in a highly chemo-, regio-, and stereoselective manner.[1] In particular, the π acidity combined with the high functional group tolerance of $Au^{I/III}$ species account for the successful application of gold catalysis in the chemical manipulation of unsaturated hydrocarbons with straightforward applications in total synthesis.[2]

Interestingly, after the pioneering enantioselective gold-catalyzed transformation reported by Ito et al. in the 1980s,[3] the chemical community did not recognize the great synthetic potential of the methodology until recently, when properly designed chiral biphenyl-type phosphine ligands have started to be efficiently coupled with Au^{I} species to perform innovative asymmetric reactions.[4]

As part of our ongoing research interests addressing the stereoselective decoration of indolyl core,[5] we recently documented the unprecedented direct activation of allylic alcohols in Friedel–Crafts alkylations by chiral gold(I) complexes (Scheme 1a).[6] Note that, despite intrinsic synthetic availability and eco-friendliness, the use of allylic alcohols as electrophilic agents in catalytic stereoselective transformations is still sporadic.[7,8] Low reactivity, the formation of carbocation intermediates, and undesirable release of water during the catalytic cycle are some of the aspects that account for such a trend.

To further validate the synthetic flexibility of the allylic alcohol/chiral Au^{I} catalyst combination, we envisioned that such a methodology could be successfully applied to the preparation of biologically relevant and stereochemically defined heterocyclic compounds (Scheme 1b).[9,10]



Scheme 1. Stereoselective gold-catalyzed synthesis of heterocyclic compounds with allylic alcohols: a) past work, b) present study.

Prompted by an interest in their pharmacological applications, we initiated our investigation with the diastereoselective synthesis of functionalized morpholines,[11] for which catalytic stereoselective synthesis still remains relatively unexplored.[12]

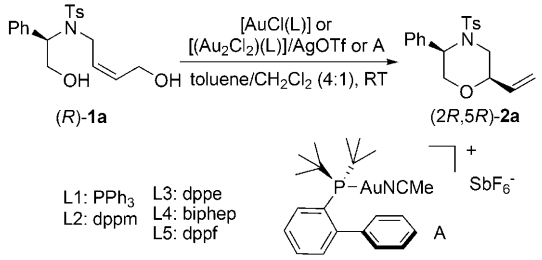
Readily available enantiomerically pure diol (*R*)-(*Z*)-**1a** (see the Supporting Information) was elected as the model substrate and a survey of reaction conditions[13] was performed to optimize the chemical and optical outcome of the intramolecular dehydrative coupling (Table 1).

Interestingly, while [$AuCl(SMe_2)$] did promote the reaction to a poor extent (yield = 46%, d.r. = 95:5; Table 1, entry 1), the introduction of a stabilizing phosphane ligand (e.g., PPh_3) led to a net increase of the final yield (Table 1, entry 2), however, a lower d.r. (83:17) value was recorded. Analogously, the well-defined silver-free gold(I)-catalyst, A,[14] induced intramolecular alkoxylation to a moderate extent (62% yield), but with poor diastereoselection (80:20; Table 1, entry 3). After screening the reaction parameters, we were delighted to find out that the chemical and stereochemical outcome of the process improved remarkably by adopting cationic dinuclear gold complexes deriving from ligands L2–L5. In particular, in situ formed $[(AuOTf)_2(L5)]$[15] complex (2.5 mol%) produced the desired *cis*-2,5-disubsti-

[a] Dr. M. Bandini, Prof. M. Monari, A. Romaniello, M. Tragni
Dipartimento di Chimica "G. Ciamician"
Alma Mater Studiorum - Università di Bologna
via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 51-2099456
E-mail: marco.bandini@unibo.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002606.

Table 1. Gold(I)-catalyzed diastereoselective synthesis of disubstituted morpholine **2a** with allylic alcohol **1a**.[a]



Entry	L or Cat. [%]	Yield [%][b]	d.r.[c]
1[d]	–	46	95:5
2[e]	L1 (10)	95	83:17
3	A (10)	62	80:20
4	L2 (5)	92	95:5
5	L3 (5)	89	95:5
6	L4 (5)	86	94:6
7	L5 (5)	93	>98:2
8[f]	L5 (2.5)	92	>98:2
9[f]	L5 (0.8)	70	98:2
10[g]	L5 (2.5)	91	97:3

[a] All of the reactions were carried out under nitrogen for 6 h, unless otherwise specified. [b] Isolated yield after flash chromatography. [c] Diastereomeric ratio (d.r.) was determined by GC analysis on the crude reaction mixture. The relative configuration was established to be *cis* by analogy to **2d** (see below). [d] Ligand-free conditions. [e] Preformed [$AuCl(PPh_3)$] was used. [f] The reaction was carried out in the absence of moisture restriction (reagent grade solvent, open-air vials with preformed [(Au_2Cl_2)(dppf)] complex). [g] Insoluble silver salts were removed by filtration. Dppm: bis(diphenylphosphino)methane; dppe: bis(diphenylphosphino)ethane; biphep: (biphenyl-2,2′-diyl)bis(diphenylposphine); dppf: 1,1′-bis(diphenylphosphino)ferrocene.

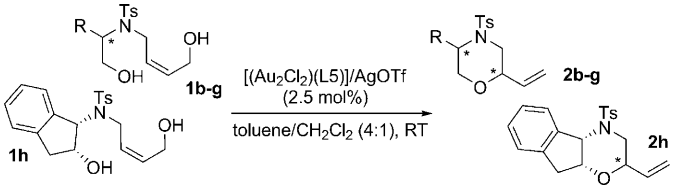
tuted morpholine **2a** in nearly quantitative yield and 98:2 d.r., without the need for any moisture restriction. Finally, [(Au_2Cl_2)(L5)] proved to be a competent precatalytic species, even at a lower catalyst loading (up to 0.8 mmol%), maintaining the stereoselection invariant (Table 1, entry 9).

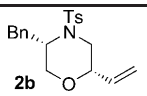
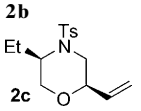
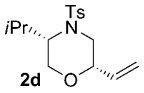
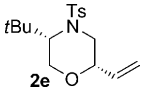
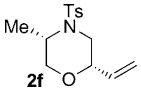
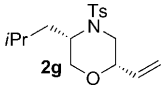
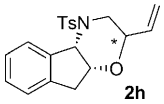
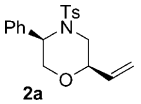
Then, the role of the silver cocatalyst in the best operating conditions was investigated by running control experiments by removing insoluble silver salts and with AgOTf as the catalytic system. Significantly, while in the first case, product **2a** was isolated in 91% yield and with high *cis* diastereoselectivity (97:3; Table 1, entry 10), the absence of gold caused the process to fail (see Table S2 in the Supporting Information for details). These findings account for the essential role of the cationic gold(I) species in triggering the catalytic process.

Encouraged by these results, we verified the generality of the method by subjecting a series of enantiomerically pure diols (**1b–h**) to dehydrative ring closure in the presence of [(Au_2Cl_2)(dppf)]/AgOTf (2.5 mol%) as the catalytic system (see Table 2).

All diols carrying sterically demanding substituents (**1b**, **d–e**, **g**) and substrates with smaller side chains (**1c**, **f**) provided the desired *cis*-2,5-disubstituted morpholines in excellent yields > 97:3 d.r. Moreover, a lower isolated yield, but excellent diastereomeric control was also recorded in the synthesis of enantiomerically pure 2,5,6-trisubstituted-tetrahydro-1,4-oxazine (**2h**; Table 2, entry 8).

Table 2. Scope of the diastereoselective gold(I)-catalyzed synthesis of morpholines.



Entry[a]	R (**1**)	Product[b]	Yield [%][b]	d.r.[c]
1	Bn (**1b**)	 **2b**	95	98:2
2[d]	Bn (**1b**)	**2b**	98	98:2
3	Et (**1c**)	 **2c**	85	98:2
4	*i*Pr (**1d**)	 **2d**	91	98:2[e]
5	*t*Bu (**1e**)	 **2e**	82	98:2
6	Me (**1f**)	 **2f**	55	97:3
7	*i*Bu (**1g**)	 **2g**	79	98:2
8[f]	– (**1h**)	 **2h**	59	98:2
9	(*E*)-**1a**	 **2a**	80	63:37

[a] All of the reactions were carried out without moisture restriction (reagent grade solvent, open-air vial) for 6 h, unless otherwise specified. [b] Isolated yield after flash chromatography. [c] Determined by GC analysis on the crude reaction mixture. [d] L4 was used as the ligand. [e] The *cis* relative configuration of **2d** was established unequivocally by means of single-crystal X-ray crystallography (see the Supporting Information). [f] Reaction time: 16 h.

Preliminary mechanistic evidence was derived by subjecting (*E*)-**1a** to optimal ring-closing conditions (Table 2, entry 9). Here, the lower stereoselection observed (d.r. 63:37) ruled out a cationic pathway,[10a] and accounted for the combined effect of 1) catalyst, 2) substrate stereocenter, and 3) substrate C=C configuration in determining the stereochemical profile of the whole process.[16]

We next sought to verify the extent of the present allylic substitution to the catalytic enantioselective synthesis of vinylmorpholines, which has rarely been reported to date.[17] To this aim, readily available compound (*Z*)-**3a** was elected as the model substrate for intramolecular dehydrative allylic alkylation. After an extensive survey of reaction conditions

(see Table S3 in the Supporting Information), [(Au_2Cl_2)\{(*R*)-3,5-*t*Bu_2-4-MeO-segphos\}] (2.5 mol%; segphos = 5,5′-bis[di(3,5-di-*tert*-butyl-4-methyoxyphenyl)phosphine]-4,4′-bi-1,3-benzodioxole), in combination with $AgNTf_2$, emerged as the best catalytic system and promoted C–O bond-forming processes. In particular, Ts-containing diol **3a** gave the desired product (**4a**) in 94% yield and 89% enantiomeric excess (Table 3, entry 1).

The *p*-methylbenzenesulfonyl substituent (Ts) proved to be crucial for efficient stereochemical translation. From an inspection of entries 1–3 in Table 3 emerges that replacing the tosyl group with (2-thienyl)sulfonyl (Ths) or mesitylsulfonyl (Mts) substituents (**3b**, **c**) leads to the corresponding cyclic compounds **4b** and **c** in high yields but lower *ee* values (69–74%). Then, we set out to examine the scope of the enantioselective gold-catalyzed process for the synthesis of vinyl-substituted morpholines that would represent one of the few examples of enantioselective gold(I)-catalyzed transformations involving unactivated olefins.[18,19]

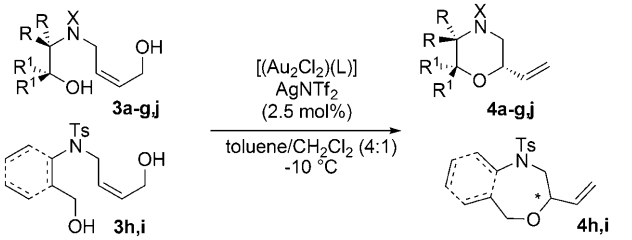
A collection of representative results is reported in Table 3. We were particularly pleased to verify the tolerance of the method toward substitutions of the acyclic precursor. In particular, it is worth mentioning that even highly sterically congested tertiary alcohols reacted smoothly under optimal reaction parameters, providing 2-vinyl morpholines in excellent yields (91–93%) and enantiomeric excesses up to 95% (Table 3, entries 5,7). The synthesis of more challenging seven-membered 1,4-oxazepanyl rings was also realized by cyclizing diols **3h** and **i**. In these cases, a higher catalyst loading (5 mol%) was required to give the corresponding products **4h**[20a,b] and **4i**[20c] in 74 and 80% *ee*, respectively (Table 3, entries 8 and 9). Finally, *N*-phenyl morpholine **4j** was also obtained with an acceptable *ee* value (76%), but with a low yield (41%) probably due to the undesired coordination of the gold atoms by tethering tertiary amine **3j** (Table 3, entry 10).

Mechanistically, several control experiments were carried out to shed light on the operating activation mode of the allylic alcohol unit by the cationic gold complex.[21]

First, as expected, a marked substrate control over stereochemical translation was discovered by subjecting diastereoisomeric (*Z*)- and (*E*)-**3a** to the optimum conditions. In particular, inversion of stereoinduction was observed in the morpholine **4a** with the same catalyst (Table 4, entry 1 vs. 2), indicating (*R*)-DTBM-segphos/(*Z*)-**3a** as the matched stereochemical combination.[22] Moreover, this inversion calls for a tight anchoring of the C=C double bond to the dinuclear catalyst with a prominent role of the hydroxyl group orientation.[23]

Interestingly, clear evidence for the direct engagement of the hydroxyl group in determining the catalytically active spatial arrangement, between starting diol and dinuclear gold complex, came from the results obtained with (*Z*)-**3a′** and **3k**–**m** (Table 4, entries 3–6). In particular, while the failure recorded with sterically demanding **3a′** can be rationalized in terms of poor π activation of the C=C double bond, the unsatisfactory stereochemical outcomes arising from **3k** and more reactive **3l** and **m** emphasized further the importance of the allylic -O*H* to obtain high ee values. Moreover, experimental evidence resulting from entries 5 and 6 in Table 4 underline the complementarity of our gold-mediated methodology with respect to classic Tsuji–Trost-like protocols.[17,24]

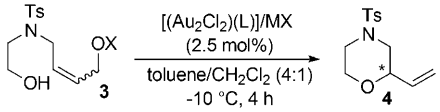
Table 3. Enantioselective gold(I)-catalyzed synthesis of heterocyclic aza-compounds.



Entry[a]	R/R_1/X (**3**)	Product	Yield of **4** [%][b]	*ee* of **4** [%][c]
1	H/H/Ts (**3a**)	**4a**	94	89
2	H/H/Ths (**3b**)	**4b**	91	69
3	H/H/Mts (**3c**)	**4c**	78	74
4	Me/H/Ts (**3d**)	**4d**	92	92
5	H/Me/Ts (**3e**)	**4e**	93	92
6	H/–$(CH_2)_4$–/Ts (**3f**)	**4f**	79	84
7	–$(CH_2)_5$–/H/Ts (**3g**)	**4g**	91	95
8[d]	**3h**	**4h**	55	74
9[d]	**3i**	**4i**	58	80
10	H/H/Ph (**3j**)	**4j**	41	76

[a] All of the reactions were carried out under nitrogen, for 4 h, unless otherwise specified. The gold complex was synthesized in situ by stirring [$AuCl(SMe_2)$] and (*R*)-DTBM-segphos (L) in CH_2Cl_2. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis with a chiral column. [d] 5 mol% of the catalyst was used at RT, reaction time 16 h. Mts: 2-mesitylsulfonyl, Ths = 2-thienylsulfonyl. The absolute configuration of **4a** was determined by comparison of the optical rotation value with that of a known compound.[17a] Moreover, the stereochemistry of **4d** was confirmed by X-ray analysis (see the Supporting Information). Absolute configuration of compounds **4b**, **c**–**e**, **g**, **j** was assigned by analogy.

Table 4. Experimental evidence for substrate control over the chemical and optical outcome of the reaction.



Entry[a]	X/C=C	MX	**4**	Yield [%][b]	*ee* [%][c]
1	H/*Z* (**3a**)	$AgNTf_2$	(*S*)-**4a**	94	88
2	H/*E* (**3a**)	$AgNTf_2$	(*R*)-**4a**	59	66
3	TBDMS/*Z* (**3a′**)	$AgNTf_2$	–	–[d]	–
4	Me/*Z* (**3k**)	$AgNTf_2$	(*S*)-**4a**	19	8
5	Ac/Z (**3l**)	$AgNTf_2$	–	–[d]	–
6	CO_2Me/Z (**3m**)	$AgNTf_2$	(*S*)-**4a**	20	7
7	H/*Z* (**3a**)	AgOTf	(*S*)-**4a**	69	68
8	H/*Z* (**3a**)	$AgSbF_6$	(*S*)-**4a**	58	50
9	H/*Z* (**3a**)	$AgBF_4$	(*S*)-**4a**	80	23
10	H/*Z* (**3a**)	NaBArF	–	trace	–
11	H/*Z* (**3a**)	AgOTs	(*R*)-**4a**	22	26
12[e]	H/*Z* (**3a**)	$AgNTf_2$	(*S*)-**4a**	71	82

[a] All of the reactions were carried out under nitrogen at −10 °C for 4 h. The gold complex was synthesized in situ by stirring [AuCl(SMe_2)] and (*R*)-DTBM-segphos (L) in CH_2Cl_2. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis with chiral column. [d] No reaction. [e] Monocationic [(Au_2Cl){(*R*)-3,5-*t*Bu_2-4-MeO-segphos}(NTf_2)] complex was used.

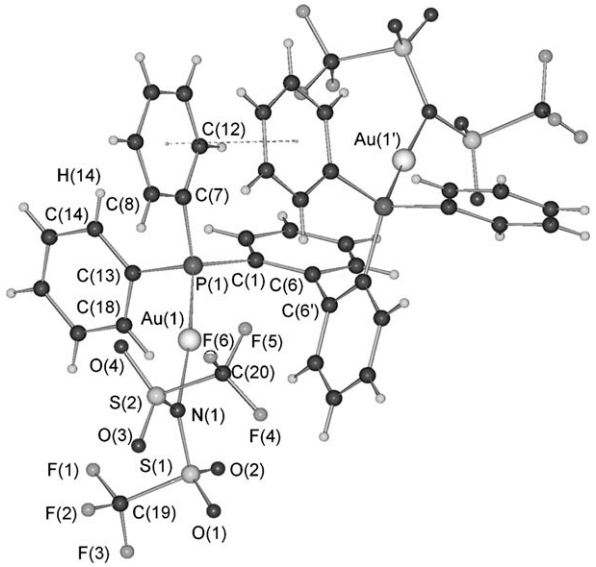


Figure 1. View of one of the molecules of the dinuclear complex [Au_2(biphep)(NTf_2)$_2$]. Relevant bond lengths and angles are listed in Table S5 in the Supporting Information.[35]

The nature of the gold counterion was also investigated by screening silver/sodium-based halide scavengers (Table 4, entries 7–11).[19a,25] Here, the collected scattering results, combined with the inversion of stereoinduction recorded with AgOTs, call for a direct involvement of the X^- species in the stereodiscriminating event of the reaction. This aspect is further corroborated by the comparable stereochemical efficiency of monocationic [(Au_2Cl){(*R*)-3,5-*t*Bu_2-4-MeO-segphos}NTf_2] in promoting the model allylic alkylation (yield = 71 %, *ee* = 82 %; Table 4, entry 12).[26] Interestingly, the chemical outcome of the reaction was also substantially affected by the type of counterion utilized and this can have reference to the well-known effect of anions over the final hydrogen-transfer (protodeauration) step of gold catalysis.[27]

With the aim to shed some light on this intriguing behavior, we first synthesized [Au_2(biphep)(NTf_2)$_2$] as a model complex, (83 % yield, see the Supporting Information for details). Suitable crystals of [Au_2(biphep)(NTf_2)$_2$] for an X-ray analysis were obtained by slow evaporation from a dilute solution of CD_2Cl_2 (4 °C, Figure 1). Two slightly different half molecules are present in the asymmetric unit around crystallographic C_2 axes passing through the midpoint of the C–C bond connecting the two twisted phenyl rings of the biphenyl unit (twist angle between phenyl rings 74.1(1)°). The two gold(I) atoms maintain the usual linear geometry and are coordinated by one P atom of the bridging biphep and by a N atom of the anionic Tf_2N^- ligand (P-Au-N 172.4 and 174.3(1)°). The Au–N (Au(1)-N(1) 2.114(4) and 2.105(4) Å) and Au–P (Au(1)-P(1) 2.227(1) and 2.225(1) Å) distances are comparable to those found in the related mononuclear [Au(NTf_2)(Ph_3P)] (Au–N 2.101(2), Au–P 2.2306(7) Å)[28] and the Au–N bonds are longer than those reported for [Au{$N(SO_2R)_2$}(PPh_3)] (R = Me, *p*-C_6H_4Cl, *p*-$C_6H_4NO_2$, F) (Au–N range 2.074-2.083 Å, Au–P range 2.222–2.230(2) Å).[29] In addition in [Au_2(biphep)(NTf_2)$_2$] the long Au···Au distances of 6.6818(6) Å (6.6829(5) Å) rule out any kind of aurophilic interaction in the solid state, which has been found in many analogous digold complexes, for example, in [(Au_2Cl_2)(biphep)] (Au···Au contact 3.0992(3) Å).[30] It may be argued that the NTf_2^- anion has a higher steric hindrance than the chloride ion. However, a digold complex bridged by biphep and having the Au^I atoms coordinated by one oxygen atom of the sterically demanding binaphthol-derived phosphate anion was reported to present a short Au···Au contact (2.9937(2) Å). The formation of intramolecular π–π stacking interactions (centroid–centroid distance 3.78 Å) between phenyl rings bound to two different P atoms (see dotted line in Figure 1) can therefore explain the lack of Au–Au contacts generated by the consequent loss of flexibility of the phosphine ligand. In fact, π–π stacking interactions between P-bound aryl rings have already been observed in [($AuCl)_2$(3,5-xylyl-binap)] (3,5-xylyl-binap = 2,2′-bis(di(3,5-xylyl)phosphino)-1,1′-binaphthyl) and an analogous digold–tol–binap (tol–binap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) complex.[31] In both cases no Au–Au interactions have been found. Finally, a further stabilization of the structure of the digold complex is given by two weak C–H···π interactions involving one hydrogen of the second phenyl ring (C(14)-H(14)···π(centroid) distance 3.03 Å) and the phenyl ring bound to the same P atom already engaged in π–π stackings. The geometry of the diphosphine-bridged digold complexes seems to be dominated by a subtle balance of noncovalent interactions that include aurophilic interactions, intramolecular π–π stacking, and ligand–ligand repulsion in addition to the flexibility of the diphosphine ligands.[32]

With the isolated complex in hand, a variable-temperature NMR spectroscopic investigation was carried out in the

presence of model substrate **3n** (see the Supporting Information). Here, although the interaction between the digold complex and **3n** was established by $^{31}P/^{13}C$ NMR spectroscopic analysis, attempts to unambiguously localize both counterions and hydroxyl groups in the $[Au_2(biphep)(NTf_2)_2]\cdot$**3n** adduct failed (VT-NMR spectroscopy and X-ray crystallography). As a consequence, we can only speculate that the second gold atom could act either as a mere spectator, perhaps stabilizing the gold intermediates through aurophilic interactions or, alternatively, being involved in a bridged arrangement through the $^{-}OH\cdots X^{-}$ network, capable of bringing steric as well as electronic diversity near the reaction site.[33]

In conclusion, we have accounted for an innovative intramolecular gold(I)-catalyzed asymmetric nucleophilic alkoxylation of allylic alcohols for the synthesis of vinyl-substituted six-/seven-membered heterocycles in a straightforward manner. Computational investigations are currently underway to clarify both activation geometry and organogold intermediates.[34]

Acknowledgements

We would like to thank the MIUR (Rome), the Università di Bologna, and the Fondazione del Monte di Bologna e Ravenna. We also thank Dr. Stefano Grilli for NMR analysis.

Keywords: alcohols · asymmetric synthesis · gold catalysis · heterocycles · stereoselectivity

[1] For general reviews on gold-catalyzed organic transformations, see: a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; c) A. S. K. Hashmi, *Catal. Today* **2007**, *122*, 211–214; d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; e) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; f) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917–4938; g) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; h) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; i) "Gold Catalysis—New Perspectives for Homogeneous Catalysis", special issue: *J. Organom. Chem.* **2009**, *649* by A. S. K. Hashmi; j) "Recent Developments in Gold Catalysis", Symposia-in-print: *Tetrahedron* **2009**, *65*, Issue 9 by F. Gagosz; k) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; l) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692–706.

[2] a) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; see also: b) K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem.* **2010**, *122*, 3595–3597; *Angew. Chem. Int. Ed.* **2010**, *49*, 3517–3519; c) Q. Zhou, X. Chen, D. Ma, *Angew. Chem.* **2010**, *122*, 3591–3594; *Angew. Chem. Int. Ed.* **2010**, *49*, 3513–3516.

[3] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

[4] a) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; b) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; c) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181; d) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609–619.

[5] a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560–566; *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; b) *Catalytic Asymmetric Friedel–Crafts Alkylations* (Eds.: M. Bandini, A. Umani-Ronchi), Wiley-VCH, Weinheim, **2009**; c) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644.

[6] M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9697–9701; *Angew. Chem. Int. Ed.* **2009**, *48*, 9533–9537; see also: M. Bandini, A. Eichholzer, A. Gualandi, T. Quinto, D. Savoia, *ChemCatChem* **2010**, *2*, 661–665.

[7] a) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315; b) C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 3200–3204; *Angew. Chem. Int. Ed.* **2007**, *46*, 3139–3143; c) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603–606; *Angew. Chem. Int. Ed.* **2008**, *47*, 593–596; d) S. Tanaka, T. Seki, M. Kitamura, *Angew. Chem.* **2009**, *121*, 9110–9113; *Angew. Chem. Int. Ed.* **2009**, *48*, 8948–8951; e) K. Namba, Y. Kaihara, H. Yamamoto, H. Imagawa, K. Tanino, R. M. Williams, M. Nishizawa, *Chem. Eur. J.* **2009**, *15*, 6560–6563; f) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* **2010**, *12*, 1184–1187; g) K. Korber, F. Rominger, T. J. J. Muller, *Synlett* **2010**, 782–786; h) M. Roggen, E. M. Carreira, *J. Am. Chem. Soc.* **2010**, *132*, 11917–11919.

[8] For general review in the use of π activated alcohols in catalytic Friedel–Crafts alkylations, see: a) M. Bandini, M. Tragni, *Org. Biomol. Chem.* **2009**, *7*, 1501–1507; b) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652–654; *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644.

[9] *Asymmetric Synthesis of Nitrogen Heterocycles* (Ed.: J. Royer), Wiley-VCH, Weinheim, **2009**.

[10] For efficient metal-catalyzed synthesis of racemic substituted tetrahydropyranes, tetrahydrofuranes, and piperidines through dehydrative cyclization of diols see: a) A. Aponick, C.-Y. Li, B. Biannic, *Org. Lett.* **2008**, *10*, 669–671; b) A. Aponick, B. Biannic, *Synthesis* **2008**, 3356–3359; c) A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond, J. Cossy, *Org. Lett.* **2010**, *12*, 1808–1811.

[11] For a general review, see: R. Wijtmans, M. K. S. Vink, H. E. Schoemaker, F. L. van Delft, R. H. Blaauw, F. P. J. T. Rutjes, *Synthesis* **2004**, 641–662.

[12] M. L. Leathen, B. R. Rosen, J. P. Wolfe, *J. Org. Chem.* **2009**, *74*, 5107–5110, and references therein. See also: a) H. Ito, Y. Ikeuchi, T. Taguchi, Y. Hanzawa, M. Shiro, *J. Am. Chem. Soc.* **1994**, *116*, 5469–5470; b) M. K. Ghorai, D. Shukla, K. Das, *J. Org. Chem.* **2009**, *74*, 7013–7022.

[13] A number of different Lewis acids were tested in the model reaction, but **2a** was always obtained to a lower extent in comparison with gold(I) catalysis, see Table S2 in the Supporting Information.

[14] a) C. Nieto-Oberhuber, S. Lòpez, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179; b) 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.

[15] T. V. Segapelo, I. A. Guzei, J. Darkwa, *J. Organomet. Chem.* **2008**, *693*, 701–708.

[16] See Figure S1 in the Supporting Information for a pictorial representation of transition states accounting for the *cis* diastereoselection.

[17] For previous examples of asymmetric Pd-catalyzed synthesis of morpholines through single and double alkylation with allylic acetates/carbonates, see: a) Y. Uozumi, A. Tanahashi, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 6826–6832; b) C. Thorey, J. Wilken, F. Hénin, J. Martens, T. Mehler, J. Muzart, *Tetrahedron Lett.* **1995**, *36*, 5527–5530; c) M. Massacret, R. Lakhmuri, P. Lhoste, C. Nguefack, F. B. B. Abelouahab, R. Fadel, D. Sinou, *Tetrahedron: Asymmetry* **2000**, *11*, 3561–3568; d) M. C. Wilkinson, *Tetrahedron Lett.* **2005**, *46*, 4773–4775.

[18] a) M. J. Johansson, D. J. Gorin, S. T. Steven, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003; b) Z. Zhang, S. D. Lee, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373; c) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057.

[19] For gold(I)-catalyzed intramolecular enantioselective hydroamination and hydroalkoxylation of allenes, see: a) R. L. LaLonde, B. D.

Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453; b) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 2887–2889; c) Z. Zhang, R. A. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287–289; *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285; d) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *129*, 14148–14149; e) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; f) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem.* **2010**, *122*, 608–611; *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601.

[20] a) L. Banfi, A. Basso, G. Guanti, N. Kielland, C. Repetto, R. Riva, *J. Org. Chem.* **2007**, *72*, 2151–2160; b) S. K. Das, A. K. Srivastava, G. Panda, *Tetrahedron Lett.* **2010**, *51*, 1483–1485, and references therein; c) H. Stadtmueller, A. Baum, G. Boehmelt, H. Engelhardt, J. Quant, F. Solca, M. Steegmaier, Z. Martin, K. Stephan, PCT Int. Appl., WO 2007096351, **2007**.

[21] H. Schmidbaur, A. Schier, *Organometallics* **2010**, *29*, 2–23, and references therein.

[22] Opposite behavior was documented in the Tsuji–Trost-type approach for the preparation of **4a**, see reference [17a].

[23] *Z* olefins have been demonstrated to bind more tightly to cationic gold(I) complexes containing sterically demanding phosphine ligands than that the corresponding *E* isomers, see: T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun.* **2009**, 6451–6453.

[24] S. Porcel, V. Lopez-Carrillo, C. García-Yerba, A. M. Echavarren, *Angew. Chem.* **2008**, *120*, 1909–1912; *Angew. Chem. Int. Ed.* **2008**, *47*, 1883–1886.

[25] For representative examples highlighting the role of silver salts as gold cocatalysts in organic transformations, see: a) M. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496; b) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123–1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; c) D. Weber, M. R. Gagné, *Org. Lett.* **2009**, *11*, 4962–4965; d) D. Zuccaccia, L. Belpassi, F. Tarantelli, A. Macchioni, *J. Am. Chem. Soc.* **2009**, *131*, 3170–3171.

[26] The complex was synthesized in situ by mixing [(Au_2Cl_2)\{(*R*)-3,5-tBu$_2$-4-MeO-segphos\}] and $AgNTf_2$ in a 1:1 ratio.

[27] G. Kovács, G. Ujaque, A. Lledós, *J. Am. Chem. Soc.* **2008**, *130*, 853–864.

[28] M. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.

[29] P. G. Jones, A. Blaschette, J. Lautner, C. Thöne, *Z. Anorg. Allg. Chem.* **1997**, *623*, 775–779.

[30] K. Aikawa, M. Kojima, K. Mikami, *Angew. Chem.* **2009**, *121*, 6189–6193; *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.

[31] a) 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; b) M. Paz Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300.

[32] D. V. Partyka, J. B. Updegraff III, M. Zeller, A. D. Hunter, T. G. Gray, *Dalton Trans.* **2010**, *39*, 5388–5397.

[33] As a partial support to the latter hypothesis, the suitability of labile counterions (i.e., OTf^-) to establish a "strong hydrogen bond with the OH from the nucleophile" in gold-catalyzed addition of phenols to olefins has been demonstrated, see: G. Kovács, A. Lledós, G. Ujaque, *Organometallics* **2010**, *29*, 3252–3260.

[34] For a recent review dealing with characterized intermediates in gold catalysis, see: A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241.

[35] CCDC-789888 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: September 9, 2010
Published online: November 18, 2010

