Gold Catalysis

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Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes

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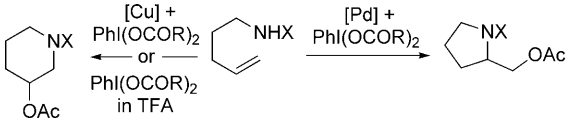
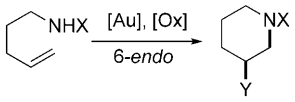
Diols, diamines, and aminoalcohols are ubiquitous functionalities in complex organic molecules. From the seminal work of Sharpless and co-workers on the intermolecular osmium-catalyzed asymmetric dihydroxylation and aminohydroxylation of alkenes,[1a,b] the development of alternative methods to access these privileged motifs has become a priority for synthetic organic chemists.[1c,d] In recent years, palladium catalysts in combination with $PhI(OAc)_2$ as oxidant have been successfully used in the aminooxygenation and diamination of unactivated alkenes both intra-[2] and intermolecularly.[3] These transformations rely on the oxidation of Pd^{II} to Pd^{IV} species to facilitate the formation of C–X bonds.[4,5] Copper-catalyzed[6] and also metal-free[7] reactions have been reported although the required acidic media in the later processes might limit its potential application in more elaborated settings [Eq. (1); TFA = trifluoroacetic acid]. Our research group has recently combined the unique carbophilicity of gold complexes with the Au^I/Au^{III} redox catalytic cycles to design new transformations.[8,9] Surprisingly, though, only one example of gold-catalyzed oxidative diamination of alkenes from ureas has been reported up to date.[10] We envisioned that highly oxidized gold(III) intermediates generated in the presence of oxidants such as Selectfluor or $PhI(OAc)_2$ could trigger the selective oxidative difunctionalization of alkenes [Eq. (2)].



(1)



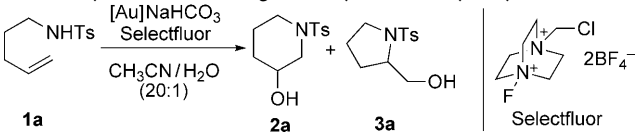
(2)

Y = OH, OMe, OAc, NHCOR, $C(sp^2)$

Herein we report the successful realization of this concept in a flexible alkene aminooxygenation reaction which allows the introduction of alcohols, ethers, or esters into the hydroamination products. We also present a novel aminoamidation process through an in situ gold-mediated activation of nitriles and an intramolecular oxidative arylation to access cumbered tricyclic benzazepine scaffolds, all based on Au^I/Au^{III} catalytic cycles.

Our study commenced with *N*-tosyl-4-pentenyl amine (**1a**) as substrate using Selectfluor as stoichiometric oxidant (Table 1).[11] The reaction in the absence of gold or with neutral $[(Ph_3P)AuCl]$ returned the starting material (Table 1,

Table 1: Optimization of the gold-catalyzed aminohydroxylation.



Entry	Modification of the standard conditions[a]	Conv. [%][b]	**2a**/**3a** ratio (Yield [%])
1	no gold, 12 h	0	–
2	$[(Ph_3P)AuCl]$, 12 h	0	–
3	**$[(Ph_3P)AuSbF_6]$, 2 h**	**100**	**9:1 (78)**
4	as in entry 3, no base	70	n.d.[c]
5	$[(Ph_3P)AuNTf_2]$, 2 h	100	9:1
6	$[(IPr)AuNTf_2]$, 12 h	0	–
7	$[\{(2,4\text{-di-}t\text{Bu}C_6H_3O)_3P\}AuSbF_6]$, 12 h	0	–
8	$[(PhO)_3PAuSbF_6]$, 12 h	50	4:1

[a] Standard reaction conditions: [Au]: 5 mol%, Selectfluor (2 equiv), $NaHCO_3$ (1.1 equiv), CH_3CN/H_2O (20:1), 0.02 M, 80 °C. [b] Measured by ^1H NMR analysis. [c] n.d.: not determined. IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylide, Tf = triflate, Ts = 4-toluenesulfonyl.

entries 1 and 2). Using a cationic $[(Ph_3P)AuSbF_6]$ complex, we were pleased to observe complete conversion of the starting material into aminoalcohols **2a** and **3a**. The reaction was highly regioselective favoring the 6-*endo*-cyclization product in a 9:1 ratio (Table 1, entry 3). In the absence of base, the reaction proved to be more sluggish (Table 1, entry 4). The counteranion in the gold complex did not influence the reaction outcome (Table 1, entry 5). In contrast, the size and electronic nature of the ligand bound to gold seemed to play an important role. Thus, the use of a bulky N-heterocyclic ligand such as 1,3-bis(2,6-diiso-propylphenyl)-imidazol-2-ylide or a more electrophilic tris-(2,4-di-*tert*-butylphenyl)-phosphite ligand completely inhibited the reaction (Table 1, entries 6 and 7). A less bulky triphenylphosphite not only slowed down the reaction but also affected the regioselectivity of the process as compared to entry 3 (Table 1, entry 8). Remarkably, under the optimized reaction conditions (Table 1, entry 3), potentially competitive processes such as protodemetalation to give 1-tosylpiperidine or β-hydrogen

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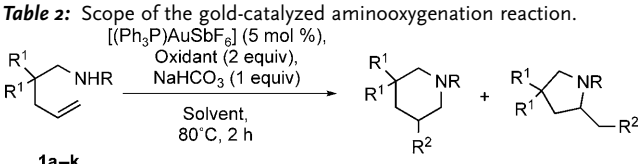
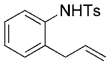
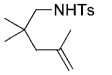
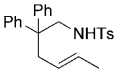
elimination to give 1-tosyl-1,2,3,4-tetrahydropyridine were never detected. We then set out to explore the scope of this *endo*-selective gold-catalyzed aminohydroxylation reaction (Table 2). First, we examined the effect of substituents in the backbone of the aminopentene substrates. *N*-Tosyl-(2,2-diphenylpent-4-enyl) amine (**1b**) reacted efficiently under

Table 2: Scope of the gold-catalyzed aminooxygenation reaction.



2 R^2 = OH **3** R^2 = OH
4 R^2 = OMe **5** R^2 = OMe
4′ R^2 = OEt **5′** R^2 = OEt
6 R^2 = OAc **7** R^2 = OAc

Entry	React. cond.[a]	Substrate, R, R^1	Products (Ratio)[b]	Yield [%][c]
1	A	**1a**: R = Ts, R^1 = H	**2a/3a** (9:1)	78[d]
2	A	**1b**: R = Ts, R^1 = Ph	**2b/3b** (9:1)	85
3	B	**1b**	**4b/5b** (9:1)	87
4	C	**1b**	**6b/7b** (4:1)	76
5	A	**1c**: R = Ts, R^1 = Me	**2c**	85
6	B′	**1c**	**4c′**	77
7	C	**1c**	**6c**	80
8	A	**1d**: R = Ts, R^1 = -$(CH_2)_5$-	**2d**	80
9	A	**1e**: 	**2e/3e** (1.5:1)	50[d]
10	A	**1f**: R = Ms, R^1 = Me	**2f**	80[e]
11	A	**1g**: R = mesitylsulfonyl, R^1 = Me	**2g**	77[e]
12	A	**1h**: R = *o*-$NO_2C_6H_4$, R^1 = Me	–	–
13	A	**1i**: R = Cbz, R^1 = Me	**2i/3i″** (1:2)	82[13]
14	C	**1j**: 	**2j**	79
15	A, B	**1k**: 	–	–

[a] Reaction conditions A: Same as Table 1, entry 3; Cond. B: Selectfluor (2 equiv), CH_3CN/MeOH (20:1), 0.02 M; Cond. B′: as B but with EtOH; Cond. C: $PhI(OAc)_2$ (2 equiv), DCE, 0.1 M, 12 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated major regioisomer. [d] Yield of the mixture of regioisomers. [e] Reaction time: 12 h. Cbz = benzyloxycarbonyl.

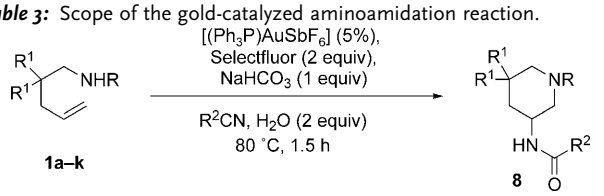
the optimized conditions to give 1,3-amino alcohol **2b** in 85% yield (Table 2, entry 2).[12] When the reaction was performed in a mixture of CH_3CN/MeOH (20:1), the corresponding aminomethoxylated product **4b** could be obtained in 87% yield (Table 2, entry 3).[2e] Switching to $PhI(OAc)_2$ as stoichiometric oxidant in 1,2-dichloroethane (DCE) as solvent, the corresponding aminoacetoxylation product **6b** was obtained in 76% yield, although lower regioselectivity was detected still favoring the piperidine product (4:1; Table 2, entry 4).

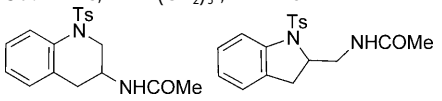
These results highlight the synthetic utility of this gold-catalyzed process, since 1,3-aminoalcohols, ethers, or acetates can be selectively obtained in a highly efficient manner through slight modifications of the reaction conditions. 2,2-Dimethyl- and 2-cyclohexyl-substituted substrates **1c–d** afforded 1,3-aminoalcohols **2c–d** in 85 and 80% yield, respectively, as single regioisomers under the standard conditions (Table 2, entries 5 and 8). The reaction of **1c** in the presence of EtOH afforded **4c′** in 77% yield whereas with $PhI(OAc)_2$ as oxidant aminoacetate **6c** was isolated in 80% yield (Table 2, entries 6 and 7). In the case of aniline **1e**, an unseparable 1.5:1 mixture of 6-*endo* and 5-*exo* aminohydroxylation products **2e** and **3e** was obtained in 50% yield (Table 2, entry 9). We then evaluated the influence of the N-protecting groups in the reaction. *N*-methyl- and *N*-mesityl-(2,2-dimethyl-pent-4-enyl) sulfonamides (**1f**, **1g**) were efficiently converted into the corresponding 1,3-aminoalcohols in good yields and complete regioselectivity (Table 2, entries 10 and 11) whereas substrate **1h** bearing an *o*-nitro-benzenesulfonyl group failed to react (Table 2, entry 12). Interestingly, the *N*-Cbz-protected substrate **1i** reacted smoothly to give the corresponding 1,3-aminoalcohol **2i** and 6,6-dimethyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-one (**3i″**) in a 2:1 ratio and 82% yield (Table 2, entry 13).[13] Internal substituted alkenes were efficiently transformed into the corresponding tertiary acetates (Table 2, entry 14).

To our surprise, when scaling up the reaction of **1b**, traces of *N*-(5,5-diphenyl-1-tosylpiperidin-3-yl)acetamide (**8b**) were detected in the mixture. In this case, the acetonitrile used as solvent reacts as a nucleophile, followed by hydrolysis to the corresponding amide. Due to the broad range of biological activities reported for *N*-piperidin-3-yl carboxamides we decided to further pursue this synthetically useful transformation.[14] After an additional short screening of reaction conditions, aminoamidation products could be selectively obtained by reducing the amount of water in the reaction to only 2 equivalents. With these new optimized conditions we studied the scope of this transformation (Table 3). Substrate **1a** afforded 1,3-aminoamide **8a** in 68% yield (Table 3, entry 1). 2,2-Diphenyl-, 2,2-dimethyl-, and 2-cyclohexyl-substituted substrates **1b–d** were efficiently transformed under these conditions into the corresponding cyclic 1,3-aminoamidation products **8b–d** in 72, 70, and 74% yield, respectively (Table 3, entries 2, 3, and 6). Aminoamide **8c** could be crystallized, thus confirming the structure of these novel derivatives (Figure 1b in the Supporting Information). Propio- and butyronitrile could also be employed (Table 3, entries 4 and 5). The reactions proved to be highly regioselective except for aniline **1e** which afforded a 1:1 mixture of regioisomers **8e** and **9e** in 70% combined yield (Table 3, entry 7). *N*-methyl and *N*-mesityl sulfonamides **1f** and **1g** afforded the corresponding products **8f** and **8g** in 64 and 46% yield, respectively, upon heating for 15 hours (Table 3, entries 8 and 9).

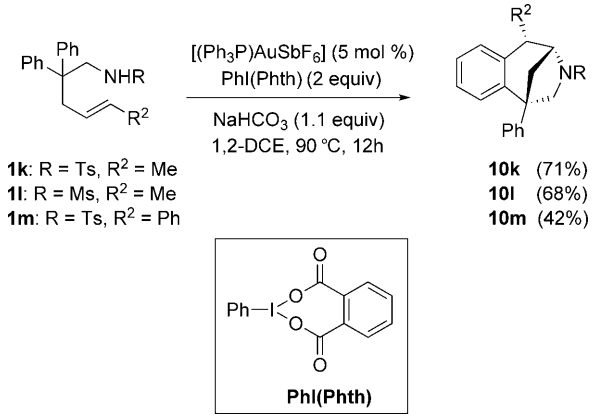
The 1,2-substitution pattern on the olefin seemed to be an intrinsic limitation for these gold-catalyzed aminooxygenation/amidation reactions (Table 2, entry 15 and Table 3, entry 10). However, the reaction of **1k** in the presence of a phthaloyl-based iodosobenzene afforded tricyclic 3-benzazepine **10k**[15] in a diastereomerically pure form as a result of the activation of one of the aromatic rings at the C_2 position of the pentene backbone (Scheme 1).[16] The reaction was extended

Table 3: Scope of the gold-catalyzed aminoamidation reaction.



Entry	1	Products: R, R^1, R^2[a]	Yield [%][b]
1	**1a**	**8a**: R = Ts, R^1 = H, R^2 = Me[c]	68[d]
2	**1b**	**8b**: R = Ts, R^1 = Ph, R^2 = Me	72
3	**1c**	**8c**: R = Ts, R^1 = R^2 = Me	70
4	**1c**	**8c′**: R = Ts, R^1 = Me, R^2 = Et	60
5	**1c**	**8c″**: R = Ts, R^1 = Me, R^2 = Pr	68
6	**1d**	**8d**: R = Ts, R^1 = -$(CH_2)_5$-, R^2 = Me	74
7	**1e**		70[d]
8	**1f**	**8f**: R = Ms, R^1 = R^2 = Me	64[f]
9	**1g**	**8g**: R = mesitylsulfonyl, R^1 = R^2 = Me	46[f]
10	**1k**	–	–

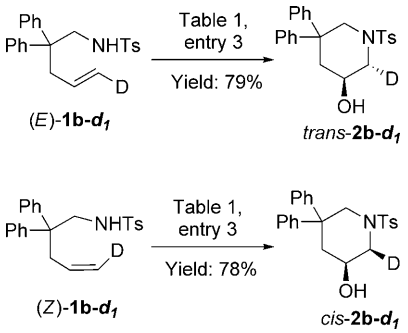
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of product isolated after column chromatography. [c] Regioisomeric mixture 9:1. [d] Yield of the isolated mixture of regioisomers. [e] Regioisomeric mixture 1:1. [f] Reaction time: 15 h.



Scheme 1. Gold-catalyzed synthesis of tricyclic 3-benzazepines.

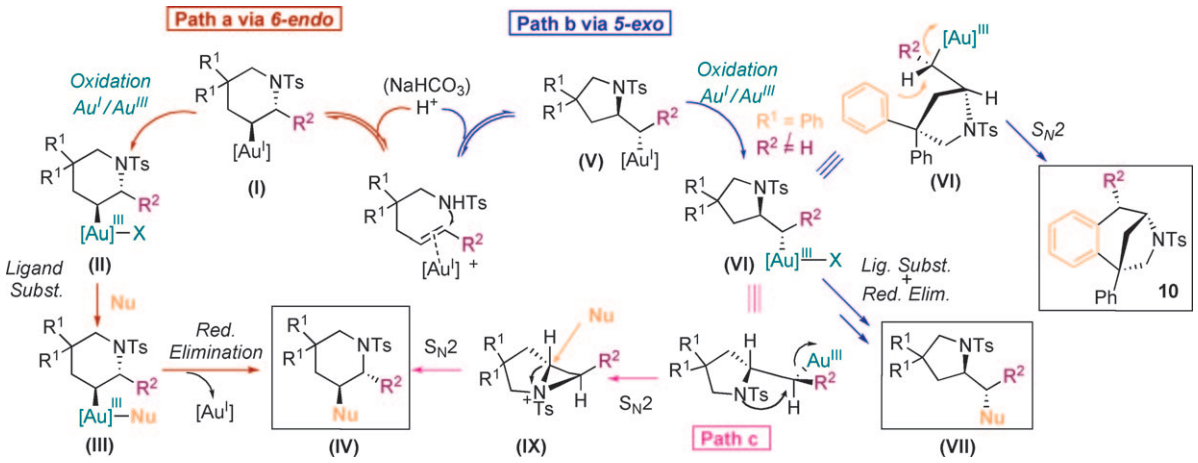
to related 1,2-disubstituted olefinic substrates **1l** and **1m**, which were converted into the tricycles **10l** and **10m** in good to moderate yields (Scheme 1). Compounds of type **10** largely incorporate the carbon framework of aphanorphines, which are marine natural compounds that resemble benzomorphane analgesics such as pentazocine.[17]

To gain a deeper insight into the mechanism of these transformations, deuterium-labeled alkenes (*E*)- and (*Z*)-**1b**-d_1 were prepared and subjected to the standard reaction conditions (Table 1), thus affording *trans*-**2b**-d_1 and *cis*-**2b**-d_1, respectively, as single diastereoisomers (Scheme 2).[18]



Scheme 2. Deuterium labeling experiments.

Based on these results, different mechanistic manifolds can be outlined as shown in Scheme 3. First, gold(I) can activate the alkene triggering the attack of the nitrogen in a 6-*endo* fashion to form **I** upon deprotonation in the presence of base in a reversible step (path a, red). The lack of reactivity of [(Ph_3P)AuCl] compared to cationic [$(Ph_3P)AuSbF_6$] supports the hypothesis of a Au^I-mediated *trans*-aminoauration of the alkene as first step in this processes.[9d,19] In addition, the failure of **1h** to react seems to rule out the hypothesis of a gold(III)–amido intermediate in contrast to copper-catalyzed processes.[6,20] Alkyl–gold(I) complex **I** can then undergo oxidation to give gold(III) intermediate **II**. If Selectfluor is used, substitution of the fluorine ligand with a suitable nucleophile such as water or alcohol delivers intermediate

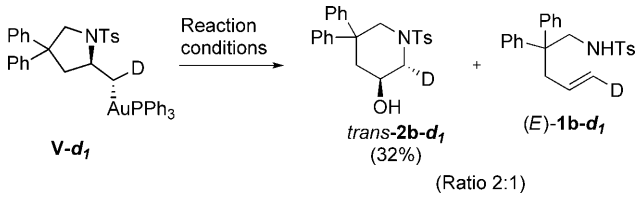


Scheme 3. Mechanistic proposals.

III.[21] Due to the highly electrophilic nature of the Au^{III} center, acetonitrile can also react as a nucleophile[22a] being hydrolyzed in the presence of water to give intermediate **III** (Nu = NHCOMe).[22b–c,23] Upon reductive elimination in **III** the new $C(sp^3)$–OH, $C(sp^3)$–OR, and $C(sp^3)$–N bonds would be formed (**IV**). If $PhI(OAc)_2$ is used as oxidant, direct reductive elimination in **II** would afford the observed aminoacetoxylation products. This proposal allows to us explain the relative configuration observed in the reactions shown in Scheme 2. Thus, no competing S_N2-type nucleophilic attack by the nucleophile on **II** would be operating in these reactions.[3,24]

In contrast, a 5-*exo* cyclization mode via intermediate **V** (Scheme 3, path b, blue) that follows a similar oxidation sequence would yield complex **VI**, thus accounting for the formation of the five-membered ring products **VII**. In fact, for 1,2-disubstituted alkenes bearing an aromatic substituent in the backbone, the aryl can behave as a nucleophile in **VI** to produce tricyclic products **10** through nucleophilic substitution reaction.

However, an alternative mechanism to explain the formation of **IV** from 5-*exo* intermediate **VI** can also be outlined (Scheme 3, path c, pink). An aziridine intermediate **IX** can be obtained from **VI** through intramolecular nucleophilic attack of the N moiety with concomitant metal departure.[25] Ring opening in the presence of an external nucleophile would afford compounds **IV**, in line with the relative configurations reported in Scheme 2. To test this hypothesis, intermediate **V-*d*$_1$**[19] was prepared and submitted to the reaction conditions affording *trans*-**2b-*d*$_1$** and (*E*)-**1b-*d*$_1$** in a 2:1 ratio (Scheme 4).[11,26] Although the transformation of **V** into **2b** is not direct evidence of its participation in the reactions described herein, it seems to indicate that several pathways can coexist under the given reaction conditions, thus explaining the formation of the observed products.



Scheme 4. Mechanistic studies.

In summary, the first gold-catalyzed aminooxygenation of unactivated alkenes and a novel alkene aminoamidation by gold activation of nitriles have been reported. The reactions are highly regioselective, thus complementing 5-*exo* palladium-catalyzed processes and expanding the scope of copper-mediated reactions. The work described herein opens up interesting mechanistic dichotomies of Au^I/Au^{III}-catalyzed transformations. In addition, tricyclic 3-benzazepines could be efficiently obtained in a diastereomerically pure form as a result of a gold-catalyzed oxidative arylation reaction. Further studies to apply the latter process to the synthesis of complex natural products are currently underway.

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[1] a) H. C. Kolb, M. S. VanNieuwenhze, B. K. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) G. Li, T.-T. Chang, B. K. Sharpless, *Angew. Chem.* **1996**, *108*, 449–452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454; c) K. Muñiz, *Chem. Soc. Rev.* **2004**, *33*, 166–174; d) T. J. Donohoe, C. K. A. Callens, A. L. Thompson, *Org. Lett.* **2009**, *11*, 2305–2307.

[2] a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691; b) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587; c) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309; d) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147–1149; during the preparation of this manuscript, a palladium-catalyzed aminoalkoxylation was reported: e) D. V. Liskin, P. A. Sibbald, C. F. Rosewall, E. M. Forrest, *J. Org. Chem.* **2010**, *75*, 6294–6296.

[3] a) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181; b) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839–5842; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737–5740.

[4] a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.

[5] See, for example: a) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142–15143; b) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard III, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807.

[6] a) P. H. Fuller, J.-W. Kim, S. R. Chemler, *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639; b) D. E. Mancheno, A. R. Thorton, A. H. Stoll, A. Kong, S. B. Blakey, *Org. Lett.* **2010**, *12*, 4110–4113; for a copper-catalyzed diamination, see: c) F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, *Angew. Chem.* **2010**, *122*, 6509–6512; *Angew. Chem. Int. Ed.* **2010**, *49*, 6365–6368.

[7] a) A. Correa, I. Tellitu, E. Domínguez, R. SanMartín, *J. Org. Chem.* **2006**, *71*, 8316–8319; b) D. J. Wardrop, E. G. Bowen, R. E. Forslund, A. D. Sussman, S. L. Weerasekera, *J. Am. Chem. Soc.* **2010**, *132*, 1188–1189; c) H. M. Lovick, F. M. Michael, *J. Am. Chem. Soc.* **2010**, *132*, 1249–1251.

[8] a) T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513; b) T. de Haro, C. Nevado, *Chem. Commun.* **2010**, DOI: 10.1039/c002679d.

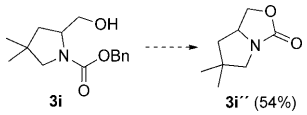
[9] For examples from other groups, see: a) H. A. Wegner, S. Ahles, M. Neuenburg, *Chem. Eur. J.* **2008**, *14*, 11310–11313; b) G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem.* **2009**, *121*, 3158–3161; *Angew. Chem. Int. Ed.* **2009**, *48*, 3112–3115; c) G. Zhang, L. Cui, Y. Wang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475; d) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard III, F. D. Toste, *Angew. Chem.* **2010**, *122*, 5651–5654; *Angew. Chem. Int. Ed.* **2010**, *49*, 5519–5522.

[10] A. Iglesias, K. Muñiz, *Chem. Eur. J.* **2009**, *15*, 10563–10569.

[11] For further experimental details, please see the Supporting Information.

[12] The structure of both regioisomers **2** and **3** could be assigned based on the X-ray diffraction analysis of compound **2b** (see Figure 1a in the Supporting Information) and by comparison with the analytical data reported for **3a** respectively: K. Miura, Katsukiyo, T. Hondo, T. Nakagawa, T. Takahashi, A. Hosomi, *Org. Lett.* **2000**, *2*, 385–388. The structure of the remaining products was assigned in analogy.

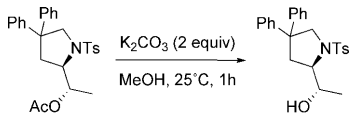
[13] The formation of **3i″** can be explained from the 5-*exo* product (**3i**).



3i **3i′′** (54%)

[14] a) E. Martini, C. Ghelardini, S. Dei, L. Guandalini, D. Manetti, M. Melchiorre, M. Norcini, S. Scapecchi, E. Teodori, M. N. Romanelli, *Bioorg. Med. Chem.* **2008**, *16*, 1431 – 1443; b) W. Yao, J. Zhuo, B. W. Metcalf, D.-Q. Qian, Y. Li, *PCT Int. Appl.* **2006**, pp. 169.

[15] In the presence of $PhI(OAc)_2$ as oxidant, pyrrolidine **7k** could be isolated in 5% yield. The relative configuration of **7k** was confirmed by X-ray diffraction of alcohol **3k**, obtained by removal of the acetoxy group under basic conditions (see Figure 1c in the Supporting Information). In addition, the structure of **10k** was also confirmed by X-ray diffraction analysis (see Figure 1d in the Supporting Information).



7k **3k**

[16] A. Tessier, A. Salisbury, G. T. Giuffredi, L. E. Combettes, A. D. Gee, V. Gouverneur, *Chem. Eur. J.* **2010**, *16*, 4739 – 4743.

[17] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, J. Clardy, *Tetrahedron Lett.* **1988**, *29*, 4381 – 4384.

[18] Similar results were obtained in the aminoacetoxylation reaction, see the Supporting Information.

[19] R. L. LaLonde, W. E. Brenzovich, D. Benitez, E. Tkatchouk, K. Kelley, W. A. Goddard III, F. D. Toste, *Chem. Sci.* **2010**, *1*, 226 – 233.

[20] S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009 – 3019.

[21] P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150 – 12154.

[22] For acetonitrile as nucleophile in gold-mediated processes, see: a) J. Barluenga, M. A. Fernández-Rodríguez, P. García-García, E. Aguilar, *J. Am. Chem. Soc.* **2008**, *130*, 2764 – 2765; for gold-catalyzed hydrolysis of nitriles, see: b) R. S. Ramón, N. Marion, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 8695 – 8697. For Pt, see: c) X. Jiang, A. J. Minaard, B. L. Feringa, J. G. de Vries, *J. Org. Chem.* **2004**, *69*, 2327 – 2331.

[23] A competition experiment was run with **1b** under conditions of Table 3 in the presence of 20 equivalents of ethyl amide. Only product **8b** was detected in the mixture, thus suggesting that acetonitrile is the actual nucleophile being hydrolyzed to the amide under the given reaction conditions.

[24] a) C. J. Jones, D. Taube, V. R. Ziatdinov, R. A. Periana, R. J. Nielsen, J. Oxgaard, W. A. Goddard III, *Angew. Chem.* **2004**, *116*, 4726 – 4729; *Angew. Chem. Int. Ed.* **2004**, *43*, 4626 – 4629. For Pd, see for example: Ref. [3b], and also b) A. T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 16354 – 16355.

[25] Aziridine intermediates have been proposed to explain the formation of 6-*endo* products in a palladium-catalyzed alkoxyamination (see Ref. [2e]). See also: E. G. Bowen, E. J. Wardrop, *Org. Lett.* **2010**, *12*, 5330 – 5333.

[26] We would like to thank one of the referees for suggesting this insightful experiment.

