CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201800042

Link to VoR: http://dx.doi.org/10.1002/chem.201800042

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Chiral Phosphine-Phosphite Ligands in Asymmetric Gold Catalysis: Highly Enantioselective Synthesis of Furo[3,4-d]-Tetrahydropyridazine Derivatives through [3+3]-Cycloaddition

Qingwei Du, Jörg-Martin Neudörfl, Hans-Günther Schmalz*[

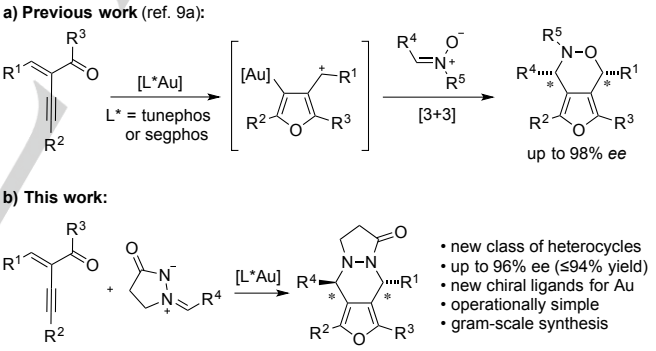
Dedicated to Prof. Stefan Toma on the occasion of his 80th birthday

Abstract: The Au(I)-catalyzed reaction of 2-(1-alkynyl)-2-alken-1-ones with azomethine imines regio- and diastereoselectively affords furo[3,4-d]tetrahydropyridazines in a tandem cyclization/intermolecular [3+3]-cycloaddition process under mild conditions. By employing a chiral gold catalyst (prepared in-situ from a Taddol-derived phosphine-phosphite ligand, Me_2SAuCl, and AgOTf) high yields and enantioselectivities (up to 94% yield, up to 96% *ee*) are obtained. The method provides an efficient modular route to substituted heterotricyclic furan derivatives and can be easily scaled up (using catalyst loads of only 0.15 mol%).

Due to the unique capability of gold(I) complexes to activate C-C multiple bonds Au-catalyzed organic transformations have emerged as efficient and powerful tools for the synthesis of complex and highly functionalized organic molecules during the past decade.[1] Noteworthy are methods for the synthesis of polysubstituted furans, which have attracted considerable attention due to the fact that the furan skeleton is found in bioactive natural products and important pharmaceuticals, and furans also represent versatile building blocks for the synthesis of more complex heterocyclic compounds.[2] However, the potential of gold catalysis in the context of heterocycle synthesis, especially with respect to the modular assembly of novel ring systems (in a diastereo- and enantioselective fashion) through intermolecular cycloaddition/annulation processes, remains an interesting challenge.

Pyridazines and their hydrogenated derivatives represent a class of heterocycles known to exhibit various kinds of biological activities including anti-tumor,[3] anti-tuberculosis,[4] analgesic,[5] and antimicrobial activities.[6] Some pyridazine-based drugs are used in the treatment of Alzheimer's, Parkinson's, and other diseases.[6b,7] Moreover, pyridazine derivatives belong to the most developable heterocyclic structures for small-molecule-based drug design.[8]

Due to their unique reactivity and easy availability 2-(1-alkynyl)-2-alken-1-ones have been used as versatile precursors in the synthesis of important heterocyclic scaffolds.[9] The first example of an Au(III)-catalyzed heterocyclization of such substrates to give polysubstituted furans was reported by Larock et al. in 2004.[10] Subsequently, Au-catalyzed heterocyclization/[3+n]-cycloaddition cascade reactions of 2-(1-alkynyl)-2-alken-1-ones to give 3,4-fused bicyclic furans were extensively investigated by Zhang[9a-f] and others.[9g-i] In this context several new reaction types were realized, however, only few examples of enantioselective Au-catalyzed transformations of 2-(1-alkynyl)-2-alken-1-ones have been reported (Scheme 1a).[9a,9d,11] Inspired by these seminal works and being aware of the importance of pyridazine derivatives in drug design, we asked ourselves whether the Au-catalyzed reaction of 2-(1-alkynyl)-2-alken-1-ones with azomethine imines[12] would open an entry to substituted furo[3,4-d]pyridazines derivatives through tandem cyclization/[3+3]-cycloaddition (Scheme 1b). We here report the successful realization of this concept and the development of a practical protocol for the atom- and step-economic synthesis of furo[3,4-d]tetrahydropyridazines in high yields and with excellent enantioselectivity (up to 96% ee). To the best of our knowledge, this is also the first example of a simultaneous construction of a furan and a hydropyridazine ring in a single synthetic operation.



Scheme 1. Au-catalyzed enantioselective tandem cyclization [3+3]-cycloaddition reactions of 2-(1-alkynyl)-2-alken-1-ones with 1,3-dipoles.

We started our investigation by probing the reaction of 2-(1-alkynyl)-2-alken-1-one **3a**[9b,10] with azomethine imine **4a**[13] in the presence of a catalyst generated in situ from Ph_3PAuCl and AgOTf. To our delight, the reaction proceeded smoothly to give the desired product *rac*-**5a** in 69% yield with a diastereoselectivity of ≥95:5 in favor of the *trans* isomer (see the Supporting Information). Encouraged by this result, we next focused on the asymmetric version of this reaction by employing chiral ligands.[14] However, several established ligands, such as DIOP, the *Trost* ligand, BINAP, Josiphos, DTBM-SEGPHOS, and phosphoramidites derived from 3,3'-disubstituted BINOLs,[15] only gave low enantioselectivities. In the best case, the product **5a** was obtained with 34% *ee* (41% yield) using a phosphoramidite ligand (for details see the Supporting Information).

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We next tested phosphine-phosphites of type **2**, a class of readily accessible modular chiral ligands, which were developed in our laboratory[16] and had shown to perform particularly well in various asymmetric transition-metal-catalyzed reactions.[17]

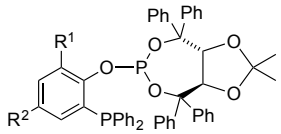

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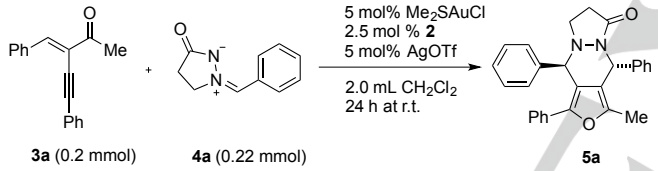
Figure 1. Chiral phosphine-phosphite ligands initially used in this study.

Remarkably, ligands of type **2** indeed performed quite well in the Au-catalyzed reaction of **3a** and **4a** under standard conditions (Table 1). Most notably, the sterically most hindered ligands **2f** and **2h** afforded the cycloadduct **5a** with encouraging yield (65-71%) and selectivity (49% and 54% *ee*, respectively) (entries 6 and 8) while ligand **2a** with a small methyl substituent in R^1 position only gave 18% *ee* (entry 1).

Table 1. Screening of chiral phosphine-phosphite ligands of type **2** in the Au-catalyzed reaction of 2-(1-alkynyl)-2-alken-1-one **3a** and azomethine imine **4a**.

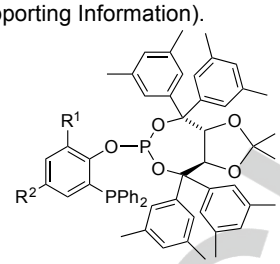


3a (0.2 mmol) **4a** (0.22 mmol) **5a**

Entry	Ligand	R^1	R^2	**5a** [%][a]	*ee* [%][b]
1	**2a**	Me	H	32	18
2	**2b**	Et	H	35	23
3	**2c**	*i*-Pr	H	48	32
4	**2d**	Ph	H	43	21
5	**2e**	*t*-Bu	H	49	42
6	**2f**	*t*-Bu	*t*-Bu	65	49
7	**2g**	*t*-pentyl	H	39	19
8	**2h**	*t*-pentyl	*t*-pentyl	71	54
9	**2i**	*t*-Bu	OMe	52	47
10	**2j**	Pr	H	49	51

[a] Isolated yield based on **3a**. [b] Determined by chiral-phase HPLC.

Employing ligands **2f** and **2h** we next investigated the effect of the solvent on the reaction outcome (Table 2, entries 1-6). While improved yields (up to 79%) and enantioselectivities (up to 67% *ee*) were observed in CH_3CN as a solvent (entries 3 and 6), the results were still not satisfying. Therefore, following our established scheme,[16] we synthesized a set of five additional and even bulkier phosphine-phosphite ligands (**2k**-**2o**) which are all derived from a Taddol carrying 3,5-dimethylphenyl substituents instead of the common phenyl units (Figure 2 and Supporting Information).

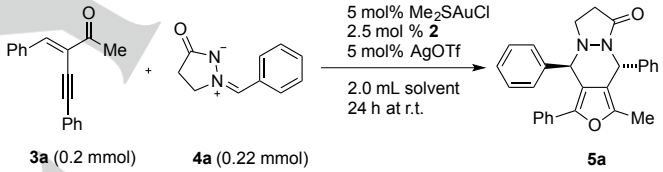


2k, R^1 = *i*-Pr, R^2 = H
2l, R^1 = Ph, R^2 = H
2m, R^1 = *t*-Bu, R^2 = *t*-Bu
2n, R^1 = *t*-pentyl, R^2 = H
2o, R^1 = *t*-pentyl, R^2 = *t*-pentyl

Figure 2. A second set of phosphine-phosphite ligands tested.

The examination of these new ligands (**2k**-**2o**) in the Au-catalyzed reaction of **3a** with **4a** under the improved conditions (Table 2, entries 7-11) revealed that the structural modification of the Taddol unit led indeed to significant changes in the reaction outcome. The substitution pattern of the ligand backbone again had a pronounced effect on the ligand performance. In this case ligand **2k** with an *iso*-propyl group in R^1 position gave better results (entry 7) than the ligands **2m**-**2o** with a bulkier tertiary R^1 substituent (entries 9-11). Using ligand **2k** the product **5a** was formed in 85% yield with a greatly improved enantioselectivity of 83% *ee*.

Table 2. Screening of different solvents and further ligands of type **2** in the Au-catalyzed reaction of **3a** with **4a.**



3a (0.2 mmol) **4a** (0.22 mmol) **5a**

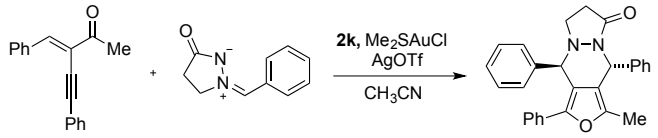
Entry	Ligand (L*)	Solvent	**5a** [%]a	*ee* [%]b
1	**2f**	CH_2Cl_2	65	49
2	**2f**	CH_2ClCH_2Cl	53	46
3	**2f**	CH_3CN	68	61
4	**2h**	CH_2Cl_2	71	54
5	**2h**	CH_2ClCH_2Cl	61	50
6	**2h**	CH_3CN	79	67
7	**2k**	CH_3CN	85	83
8	**2l**	CH_3CN	76	59
9	**2m**	CH_3CN	71	69
10	**2n**	CH_3CN	69	58
11	**2o**	CH_3CN	70	72

[a] Isolated yield based on **3a.** [b] Determined by chiral-phase HPLC.

Having identified **2k** as the most suitable ligand for the enantioselective synthesis of **5a**, we further optimized the reaction by varying the temperature and the amount of catalyst. As the results shown in Table 3 indicate, a significant decrease of the enantioselectivity was observed upon raising the reaction temperature from r.t. to 40 °C. In contrast, decreasing the

reaction temperature had no major effect on the enantioselectivity, only the yield dropped slightly (Table 3, entries 1-4). Therefore, all following reactions were run at r.t. Not surprisingly, the amount of catalyst was found to mainly influence the yield (conversion) while the enantioselectivity was little affected (Table 3, entries 2 and 5-7). The best result was obtained with 5 mol% of the catalyst generated in situ from equimolar amounts of **2k**, Me_2AuCl, and AgOTf.

Table 3. Effects of temperature and amount of catalyst on the Au-catalyzed reaction of **3a** with **4a.**



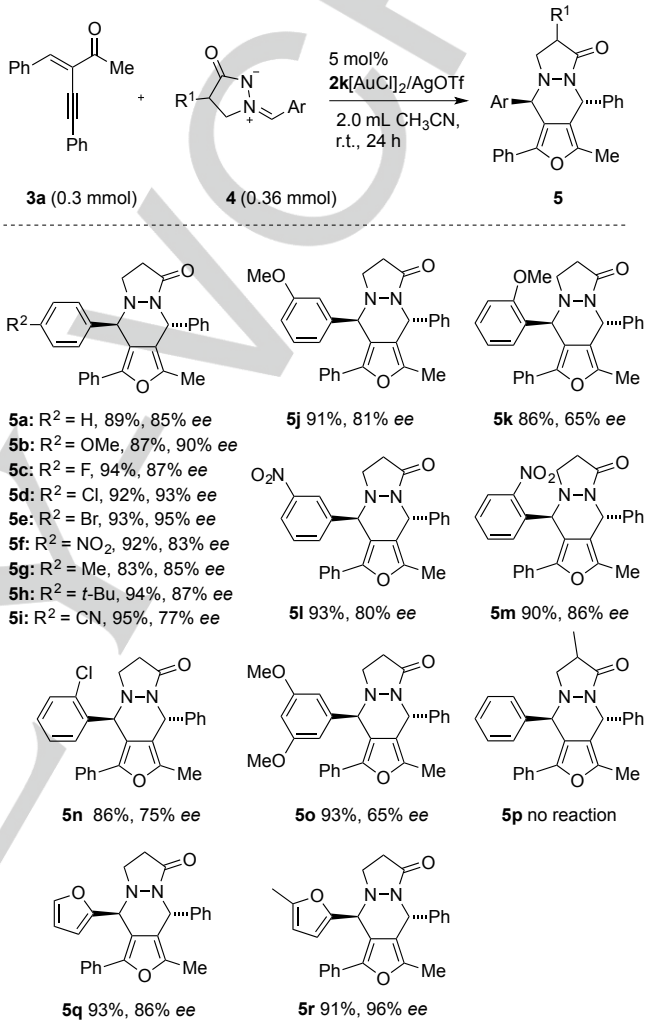
3a (0.2 mmol) **4a** (0.22 mmol) **5a**

Entry	Temp. (°C)	L*[AuCl]$_2$ (mol%)	AgOTf (mol%)	**5a** [%][a]	*ee* [%][b]
1	40	2.5	2.5	87	73
2	r.t.	2.5	2.5	85	83
3	-10	2.5	2.5	72	84
4[c]	-20	2.5	2.5	59	82
5	r.t.	1.25	1.25	43	80
6	r.t.	5	5	89	85
7	r.t.	7.5	7.5	86	83
8	r.t.	5	7.5	81	79
9	r.t.	5	10	82	69
10[d]	r.t.	5	5	87	80

Conditions: x mol % of in situ formed catalyst (**2k**/Me_2SAuCl = 1:2), CH_3CN 2.0 mL, 24 h. [a] Determined by GC-FID. [b] Determined by chiral-phase HPLC. [c] Reaction was run for 32 hours. [d] **2k**/Me_2SAuCl = 1.1:2.

Recent reports suggested that gold complexes of type L_2Au_2ClX with a weakly bound anion X, generated in situ from a 1:1 mixture of $[L_2Au_2Cl_2]$ and an AgX activator, may give better enantioselectivities than bicationic $[LAu_2X_2]$ species.[9a,18] However, changing the **2k**$[AuCl]_2$/AgOTf ratio from 1:1 to 1:2 only resulted in a slight decrease of the enantiomeric excess of the product **5a** (Table 3, entry 10).

Taking the optimized conditions (Table 3, entry 6) as a standard, we now explored the substrate scope of this novel cycloaddition by reacting **3a** with various azomethine imines **4** (Scheme 2). Much to our delight, the products of type **5** were obtained in most cases in high yield (83%-95%) and with good to excellent enantioselectivity (65-96% *ee*). As the results shown in Scheme 2 indicate, the reaction worked reliably with a broad range of substrates of type **4** independent of the nature of the aryl (or heteroaryl) substitutent. Only an α-methylated substrate (**4p**) failed to give the expected product **5p**. The relative (*trans*) configuration of the products was initially proven by X-ray crystal structure analysis of *rac*-**5a** and *rac*-**5f** (see the Supporting Information), and in the case of **5e** and **5r** the absolute configuration could also be determined this way (Figure 3). We assume all products of type **5** prepared using **2k** as a chiral ligand belong to the same series of absolute configuration. This is additionally supported by the fact that all products showed a related chiroptical behavior (with usually positive [α] values at 436 nm which decrease or even become negative at larger wavelengths).



Scheme 2. Au-catalyzed reaction of **3a** with various azomethine imines **4**. Yields refer to isolated products. Enantiomeric purities (*ee*) were determined by chiral-phase HPLC.

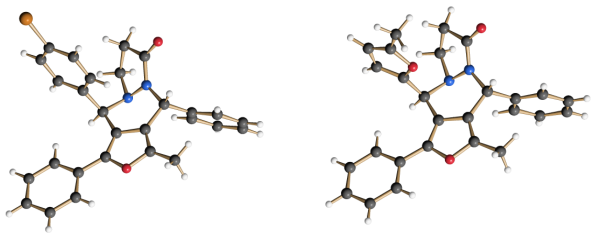
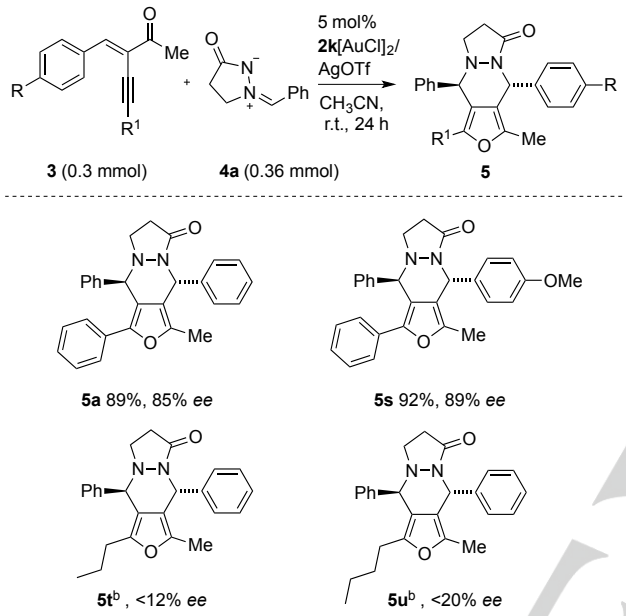


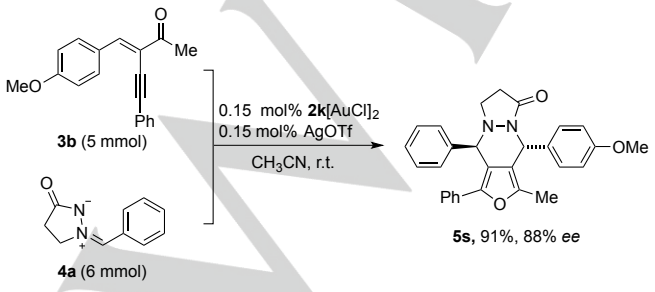
Figure 3. Structures of **5e** (left) and **5r** (right) in the crystalline state.[19]

The scope of the developed method was further investigated by employing differently substituted 2-(1-alkynyl)-2-alken-1-ones (Scheme 3). While the 4-*para*-methoxyphenyl substituted product **5s** was formed even with improved *ee* (as compared to the parent product **5a**), replacement of the phenyl group by aliphatic R^1 substituents at the alkyne resulted in a dramatic decrease of the enantioselectivity and the cycloaddition products **5t** and **5u** were obtained only in ≤12% *ee* and ≤20% *ee*, respectively, as major components of inseparable mixtures. Here some limitations of the method become apparent.



Scheme 3. Au-catalyzed reaction of different 2-(1-alkynyl)-2-alken-1-ones (**3**) with azomethine imine **4a**. [a] Yields refer to isolated products. Enantiomeric purities (*ee*) were determined by chiral-phase HPLC. [b] Main component of an inseparable product mixture.

Finally, to demonstrate the preparative usefulness of the developed methodology we applied it in a gram-scale synthesis of the furo[3,4-d]tetrahydropyridazine **5s** (Scheme 4). In this transformation the catalyst loading could be reduced to 0.15 mol% on a 5 mmol scale without any loss of selectivity and efficiency providing **5s** in 91% yield with an enantiomeric excess of 88% *ee*.



Scheme 4. Gram-scale synthesis of the furo[3,4-d]pyridazine **5s**.

In conclusion, we have discovered and developed a novel gold-catalyzed transformation of 2-(1-alkynyl)-2-alken-1-ones with azomethine imines furnishing highly substituted furo[3,4-d]tetrahydropyridazines as a new type of heterocyclic system. The tandem cyclization/[3+3]cycloaddition process was shown to proceed with virtually complete regio- and diastereoselectivity to give the products in good to excellent yields and with up to 96% enantiomeric excess. The key for this success was the identification of the new chiral phosphine-phosphite ligand **2k** as a most suitable catalyst precursor, which performed superior in comparison to other established ligands in asymmetric gold catalysis. Other salient features of the developed method include operational simplicity and mild conditions, easy accessibility of substrates, functional group tolerance, and scalability (with a catalyst loading of only 0.15 mol% of catalyst on a gram scale). Thus, the developed method might find future application in the stereoselective synthesis of furo[3,4-d]-pyridazines as potentially bioactive compounds. In addition, the demonstrated potential of our phosphine-phosphite ligands (such as **2k**) might be of interest to other researchers working in the active field of asymmetric gold catalysis.

Acknowledgements

This work was supported (doctoral fellowships to Q. Du) by the China Scholarship Council and the Deutscher Akademischer Austausch Dienst (DAAD). We gratefully thank Dipl. Ing. Andreas Adler for performing the HPLC measurements.

Keywords: Gold • Enantioselective Catalysis • Chiral Phosphorous Ligands • Heterocyclic Compounds • 1,3-Dipoles

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10.1002/chem.201800042

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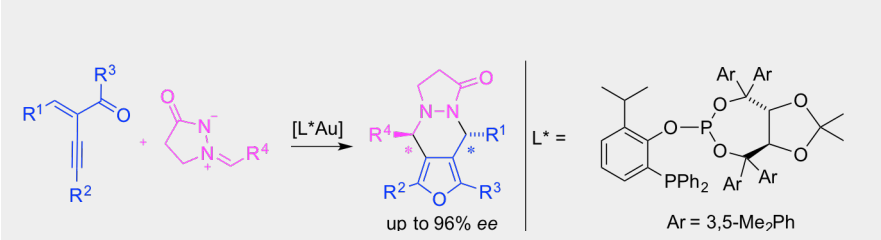

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