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Gold catalyzed enantioselective intermolecular [3+2] dipolar cycloaddition of *N*-allenyl amides with nitrones†

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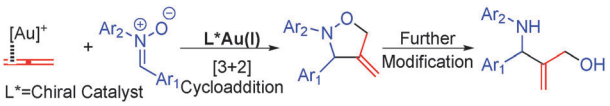
A gold catalyzed enantioselective [3+2] dipolar cycloaddition of *N*-allenyl amides with nitrones was developed to give chiral 4-alkylidenyl isoxazolidine derivatives in high yields and excellent enantioselectivities by using BINOL derived chiral phosphoramidate Au(I) catalysts.

Stereoselective 1,3-dipolar cycloadditions of nitrones with C–C unsaturated bonds have long been the topic of many studies.[1] In particular, the asymmetric nitrone–alkene cycloadditions have received a great deal of attention. Various chiral metal complexes[2] as well as organic catalysts[3] were devised for this transformation. Moreover, enantioselective 1,3-dipolar nitrone–alkyne cycloadditions using chiral Cu(II) catalyst or organocatalysts were documented.[4] However, the asymmetric nitrone–allene dipolar cycloaddition reaction is not reported yet.[5] This may be due to the challenge posed by the substrate requirement in the previous methods.[2–4]

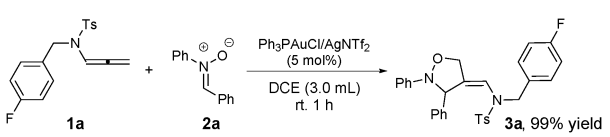
Recent advances in gold chemistry provided new opportunities for allene's asymmetric transformation.[6] The initial examples of enantioselective gold catalyzed allene cycloadditions are exclusively intramolecular reactions.[7,8] In the process of this research, two intermolecular asymmetric reactions, including [2+2][9a] and [4+2][9b] cycloaddition of allenes with alkenes or dienes, were also achieved.[9] Nevertheless, all these reports focused on the preparation of the carbocycle products. We herein disclosed the first example of gold catalyzed enantioselective intermolecular [3+2] dipolar cycloaddition of *N*-allenyl amides[10] with nitrones[11] by using BINOL derived chiral phosphoramidate Au(I) catalysts[12] to give chiral 4-alkylidenyl isoxazolidine derivatives in high yields and excellent enantioselectivities (Scheme 1). Further modification of isoxazolidines **3a** and **3f** through a coupling reaction and RANEY®-Ni reduction provided chiral 1,3-amine alcohol derivatives in high yields.



Scheme 1 A 1,3-dipolar cycloaddition–reduction sequence to give chiral amino alcohols *via* isoxazolidine.

The reaction of tosyl *N*-allenyl amide **1a** with diphenyl nitrone **2a** was chosen for our initial investigation. After a series of experiments, $Ph_3PAuCl/AgNTf_2$ shows to be the best catalyst combination in DCE to give the desired dipolar cycloadduct **3a** in almost quantitative yield (Scheme 2).[13]

Based on the optimized result of this racemic reaction, we started to identify an effective chiral ligand for this new [3+2] dipolar cycloaddition. At first, the chiral diphosphine ligand **L1** was tested, but it gave no desired product (Table 1, entry 1). Spiro ligands **L2** and **L3** were then evaluated. The (*R*)-1,1′-spirobiindane-7,7′-diol derived (*R*)-SIPHOS **L2** provided **3a** in a moderate yield with 33% ee (Table 1, entry 2), while (*R*)-SIPHOS-PE **L3**, with a (*R*,*R*)-bis(1-phenylethyl) amine moiety in the ligand, gave a reversed enantioselectivity (−31% ee, Table 1, entry 3). This meant that the chiral bis(1-phenylethyl)amine unit played an important role in **L3**'s asymmetric transition state. A similar phenomenon, though not so evident, could be observed in experiments using BINOL derived phosphoramidate ligands **L4**, **L5** and **L6**. **L5** and **L6** gave the same major enantiomer as **L4** did, while (*R*,*R*)- or (*S*,*S*)-bis(1-phenylethyl)amine units enhanced or decreased **3a**'s enantioselectivity (Table 1, entries 4–6). These results indicated that the (*R*)-BINOL unit played a major role in the asymmetric induction process, which could be reinforced or weakened by the chiral amine moiety. We envisioned that further modification of the



Scheme 2 Racemic [3+2] dipolar cycloaddition.

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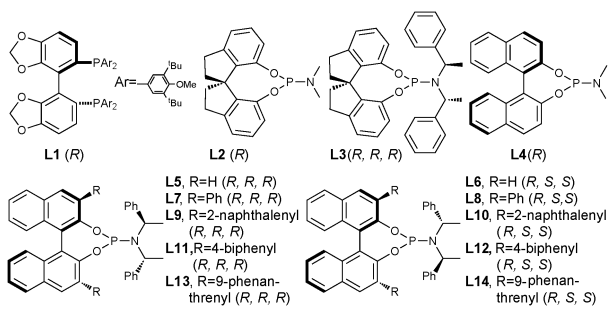
Table 1 Optimization studies of the enantioselective [3+2] dipolar cycloaddition of **1a** and **2a**[a]

Entry	L*	Sol/temp. [°C]	*t* [h]	Yield [%]	ee[b] [%]
1	**L1**	DCE/rt	20	NR	
2	**L2**	DCE/rt	5.5	59	33
3	**L3**	DCE/rt	2.5	76	−31
4	**L4**	DCE/rt	3	84	24
5	**L5**	DCE/rt	2	79	40
6	**L6**	DCE/rt	5	73	9
7	**L7**	DCE/rt	4	84	87
8	**L8**	DCE/rt	5	57	27
9	**L9**	DCE/rt	5	66	50
10	**L10**	DCE/rt	3	83	20
11	**L11**	DCE/rt	2	85	67
12	**L12**	DCE/rt	20	NR	
13	**L13**	DCE/rt	1	90	92
14	**L14**	DCE/rt	20	NR	
15[c]	**L13**	DCE/−20	4.5	99	94
16[c]	**L13**	DCM/−20	4.5	99	98
17[c,d]	**L13**	DCM/−20	10	74	98
18[c,e]	**L13**	DCM/−20	10	99	98

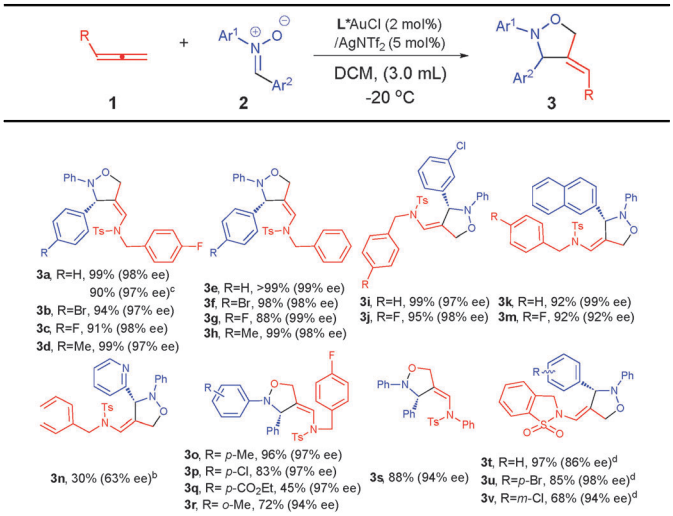
[a] Unless noted, all reactions were carried out at a 0.1 mmol scale in 3 mL solvent with the addition of 5 mol% catalyst at −20 °C, NR = no reaction. [b] The ee value was determined using HPLC on a Chiralpak AD-H column (see ESI). [c] 100 mg 4 Å MS was added. [d] 2 mol% catalyst was used. [e] 2 mol% **L13**AuCl and 5 mol% $AgNTf_2$ were added.

BINOL unit by placing bulky groups at the 3,3′-position of BINOL would improve its asymmetric induction level.[14] To our delight, 3,3′-diphenyl substituted (*R*,*R*,*R*)-**L7** provided a much higher enantioselectivity, in contrast to the poor performance of its (*R*,*S*,*S*)-isomer **L8** (Table 1, entries 7 and 8). Although 2-naphthalenyl and 4-biphenyl ligands (*R*,*R*,*R*)-**L9** and (*R*,*R*,*R*)-**L11** did not further improve the enantioselectivity, 9-phenanthrenyl substituted (*R*,*R*,*R*)-**L13** provided the desired cycloadduct (*S*)-**3a** in 90% yield with 92% ee (Table 1, entries 9, 11, and 13). Nevertheless, the cycloaddition did not proceed in the presence of (*R*,*S*,*S*)-**L12** and (*R*,*S*,*S*)-**L14**, possibly because of the strong opposing effects of the two chiral units (Table 1, entries 12 and 14). Temperature and solvent were subsequently optimized. The best result was obtained in DCM at −20 °C with the addition of 100 mg 4 Å MS to give **3a** in 99% yield and 98% ee (Table 1, entries 15 and 16). Decreasing the catalyst loading to 2 mol% led to a reduced reaction yield (Table 1, entry 17). We considered that gold–nitrone coordination might impair the activity of the gold catalyst. A slightly excessive amount of $AgNTf_2$ (5 mol%) was then added under the conditions of 2 mol% of **L13**AuCl, and it was found that the desired product **3a** can be obtained in almost quantitative yield and high enantioselectivity after 10 h of reaction (Table 1, entry 18).‡[15]



With the optimized reaction conditions in hand, we then examined the substrate scope. At first, nitrones with different

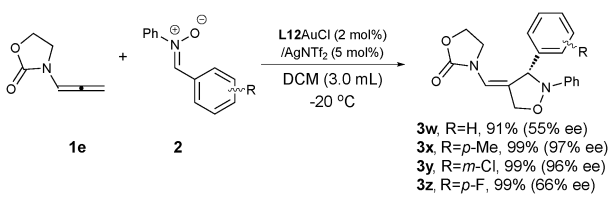
Table 2 The representative 1,3-dipolar cycloaddition reactions for various *N*-allenylic sulfonamides and nitrones[a]



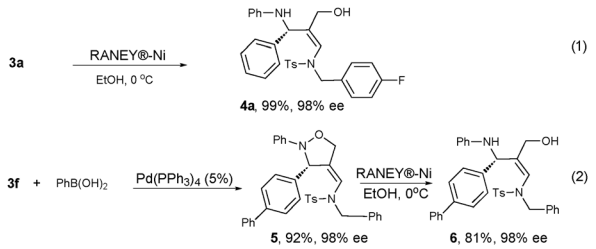
[a] Unless noted, all reactions were carried out at a 0.1 mmol scale in 3 mL DCM with the addition of 2 mol% **L13**AuCl, 5 mol% $AgNTf_2$ and 100 mg 4 Å MS at −20 °C. [b] 0.5 equiv. of $AgNTf_2$ was utilized. [c] 1 mmol scale reaction was performed. [d] **L9** was utilized as the chiral ligand.

substitution patterns were tested by using *N*-allenyl *p*-fluorobenzyl sulfonamides (**1a**) or *N*-allenyl benzyl sulfonamides (**1b**) as the reaction partners. As shown in Table 2, both electron donating and mild electron withdrawing substituted nitrones gave the desired isoxazolidines in good to excellent yield with a high level of enantioselectivities (for the Ar^2 group: **3a–3h**, **3i–3m**, for the Ar^1 group: **3o** and **3p**, Table 2).[16] However, pyridinyl nitrone exhibited a poor reactivity, possibly due to the coordination of the chiral auric cation with pyridine (**3n**, Table 2). Low yields were also obtained in the reactions of *p*-esteryl with *o*-methyl substituted phenyl nitrones, where high levels of asymmetric induction were still maintained (**3q–3r**, Table 2). In the reactions of cyclic *N*-allenyl sulfonamides with various nitrones, **L9** was found to be the optimal chiral ligand. The corresponding cycloadducts were thus synthesized in good yields and excellent enantioselectivities (**3t–3v**, Table 2). In addition, a 1 mmol scale reaction of **1a** with **2a** was performed, giving **3a** in 90% yield with 97% ee.

Next, the reaction of oxazolidin-2-one derived *N*-allenyl oxazo-lidin-2-one **1e** was investigated, in which ligand **L12** could provide the best enantioselective induction. Although cycloaddition of **1e** with diphenyl nitrone **2a** gave isoxazolidine **3w** with a low ee value (**3w**, Scheme 3), the presence of a substituent on the phenyl group greatly enhanced the enantioselectivity of the product. *p*-Methyl or *m*-chloro substituted nitrones provided the corresponding cycloadducts **3x** and **3y** in excellent enantioselectivities (**3x–y**, Scheme 3). The poor performance of **3z** might be due to the small size of the fluoro group.



Scheme 3 Enantioselective [3+2] dipolar cycloadditions of oxazolidin-2-one derived *N*-allenyl amide **1d** with nitrones.



Scheme 4 Further modification of **3a** and **3f** through a coupling reaction and RANEY®-Ni reduction

1,3-Amino alcohol motifs are important structural elements in a diverse range of natural products and pharmaceuticals, which can be prepared from isoxazolidines through a ring opening reaction.[17] With our established enantioselective intermolecular [3+2] cycloaddition of *N*-allenyl amides with nitrones, the N–O bond fission reaction of cycloadducts **3** *via* reduction was then investigated. After a brief screening of several reductants, it was found that isoxazolidine **3a** could be reduced by RANEY® nickel efficiently in ethanol at 0 °C, furnishing the desired amino alcohol **4a** in 99% yield and 98% enantioselectivity (Scheme 4, eqn (1)).[18] Coupling of **3f** with phenyl boronic acid, followed by RANEY® nickel reduction, provided biphenyl functionalized amino alcohol product **6** (Scheme 4, eqn (2)). High enantioselectivity was still maintained after two steps of reactions.

In summary, we have demonstrated a novel and practical protocol of gold-catalyzed enantioselective intermolecular [3+2] dipolar cycloaddition of *N*-allenyl amides with nitrones to give chiral isoxazolidines by using modified BINOL derived chiral phosphoramidate Au(I) catalysts, in which an excessive amount (5 mol%) of silver salts were added to reduce the undesired gold–nitrone coordination and to enhance the catalytic activity of the auric cation. Further derivation of compounds **3a** and **3f** could provide two chiral 1,3-amino alcohols **4a** and **6** in high enantioselectivities. This is the first report, to the best of our knowledge, on enantioselective allene–nitrone cycloaddition to give chiral 4-alkylidenyl isoxazolidine derivatives in excellent yields and high enantioselectivities.

Notes and references

‡ General procedure for the enantioselective gold catalyzed [3+2] cycloaddition reaction of *N*-allenyl amides with nitrones: a solution of **L13**AuCl (2 mol%)/$AgNTf_2$ (5 mol%) in dry CH_2Cl_2 (3 mL) with 100 mg activated 4 Å MS was stirred at rt for three minutes. Then, *N*-allenyl amide **1a** (32 mg, 0.1 mmol) and diphenyl nitrone **2a** (39 mg, 0.2 mmol) were added to the solution at −20 °C. The mixture was stirred at −20 °C until complete consumption of the starting material **1a** (TLC monitoring). The concentration of the reaction mixture *in vacuo* followed by purification through flash chromatography (hexane–EtOAc = 10/1) afforded **3a** (51 mg, 99% yield) as a white solid.

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