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Catalytic Three-Component Domino Reaction for the Preparation of Trisubstituted Oxazoles

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Abstract: Multicomponent reactions are attractive for assembling functionalized heterocyclic compounds. To this end, an efficient gold-catalyzed three-component domino reaction to form oxazoles directly from imines, alkynes, and acid chlorides is presented. The reaction proceeds in a single synthetic step by using a gold(III)–*N*,*N*′-ethylenebis(salicylimine) (salen) catalyst to give trisubstituted oxazoles in up to 96% yield. The substrate scope, a mechanistic study exploring the role of the gold catalyst, and the synthetic applications of the oxazole products are discussed.

Keywords: gold · heterocycles · homogeneous catalysis · multicomponent reactions · oxazoles

Introduction

Oxazoles constitute key structures in functional molecules with diverse applications ranging from synthetic intermediates[1] to fluorescent probes,[2] peptidomimetics,[3] and new materials.[4] They are represented in natural products with cytotoxic and antimicrobial properties,[5,6] as exemplified by the nanomolar-active ajudazol.[7] In medicinal chemistry, oxazoles are found in anti-inflammatory, antiviral, and analgesic agents.[8] Classical methods for oxazole synthesis include dehydration of α-keto amides under forcing conditions.[6,9] Recent examples of oxazole synthesis by intermolecular reactions include the addition of α-isocyanates to imines,[10a,b] cycloadditions of acyl azides to alkynes,[10c] and transition-metal-catalyzed [3+2] cycloadditions.[10d,e] Methods based on the cyclization/isomerization of propargyl amides have been widely studied. Variations are plentiful and include the use of alkynyl alanes,[11a] palladium salts,[11b–d] gold salts,[11e–h] cerium salts,[11i] hypervalent iodine,[11j] Lewis acids,[11k] and Brönsted acids.[11l] Additional cyclization reactions to form oxazoles include the reaction of α-amino ketones and aldehydes,[12a] the reaction of alkynes and amines followed by in situ oxidation,[12b] and oxidative gold- or copper-catalyzed[12c,d] reactions between alkynes and nitriles.[13]

A powerful tool for the rapid generation of molecular complexity is the multicomponent reaction (MCR). Domino MCRs to form oxazoles are rare and are often based on the Van Leusen oxazole synthesis or Ugi-like reactions with isocyanates followed by in situ cyclization.[14] More common procedures rely on telescoping, in which the consecutive addition of reactants and/or reagents gives the oxazole product in one pot.[15] A convenient MCR to generate propargyl amines with potential use as oxazole precursors is the catalytic addition of alkynes to imines formed in situ (^{3}A coupling). The reaction proceeds with a range of catalytic systems including the use of copper,[16a] silver,[16b] zinc,[16c] iron,[16d] indium,[16e] iridium,[16f] and gold salts.[16g] An extension of this methodology for the direct formation of propargyl amides from alkynes and nonenolizable imines in the presence of acyl chlorides was reported by Black and Arndtsen.[17] Conceptually, the bridging of complexity-generating processes, such as catalytic acetylide addition to imines and catalytic cycloisomerizations, in a single multicomponent domino reaction is an attractive approach for the assembly of multifunctionalized structures.[18] The present art is, however, limited to processes that incorporate the substituents on the imine nitrogen atom into the final product. This limits the scope of the hetereocycles accessible through this strategy, and consequently, it has not been used for oxazole synthesis. Herein, we present a catalytic reaction that produces oxazoles directly from readily available *N*-benzylimines and commercially available alkynes and acyl chlorides (Scheme 1). Under optimized conditions, the reaction produces trisubstituted oxazoles displaying diverse functional groups in up to 96% yield by using as little as 1 mol% of a gold(III)–salen catalyst and with a reaction time of only 15 min.

The essence of the title reaction is captured in Scheme 1. At the outset, we envisioned that a single metal complex would serve as a catalyst (or a precatalyst) to mediate three consecutive processes: 1) an acyl iminium–alkyne coupling to form a propargyl amide, 2) activation of the alkyne for cyclization to form the penultimate five-membered ring, and 3) isomerization of the *exo*-alkene formed in the cyclization step to give the desired oxazole. The overall process would be enabled by the loss of the sacrificial imine benzyl group

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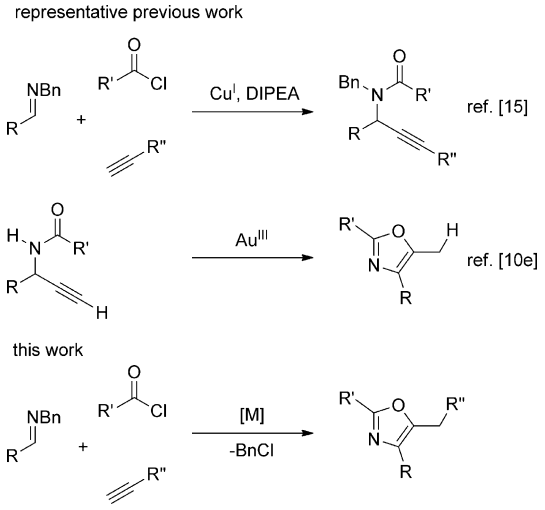


Scheme 1. Transition-metal-catalyzed synthesis of oxazoles and their precursors. DIPEA = *N*,*N*-diisopropylethylamine.

in the form of benzyl chloride.[19] A conceptually related procedure for the asymmetric synthesis of cyclic carbamimidates was recently presented.[20]

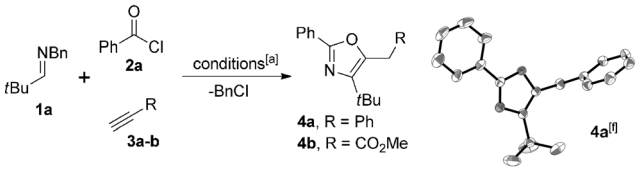
Results and Discussion

Optimization of the reaction was done with *tert*-butyl-*N*-benzylimine (**1a**) as the imine component, and the results are summarized in Table 1. In the presence of phenylacetylene and benzoyl chloride with gold(III) chloride as the catalyst, the desired oxazole **4a** was formed in moderate yield (Table 1, entry 1). In solvent (acetonitrile), the yield was improved to 70%, but the reaction was accompanied by extensive deposition of metallic gold. When the metal was stabilized with a salen ligand in the form of [Au(salen)]PF_6, a catalyst previously shown to efficiently catalyze ^{3}A couplings in water,[21] oxazole **4a** was obtained in essentially quantitative yield by using as little as 1 mol% of the catalyst (entry 7).[22]

The continuous removal of chloride ions from the reaction mixture in the form of benzyl chloride is an important feature of the reaction because it preserves the activity of the gold catalyst. In a control experiment with gold(III)–salen chloride as the catalyst, the yield was reduced to 50% for the reaction between *t*Bu-*N*-benzylimine, phenylacetylene, and benzoyl chloride. Solvents other than MeCN (dioxane, toluene, and dichloroethane) were screened, but all resulted in a decreased yield. Additives like bases (Et_3N and di-*tert*-butylpyridine) to promote the metal–acetylide formation led to decomposition, and a Lewis acid ($Zn(OTf)_2$)[23] gave a decreased yield. Under the optimized conditions, the reaction can be scaled by an order of magnitude without loss of efficiency, and on over a gram scale, oxazole **4a** was crystallized directly from the reaction mixture in 80% yield through addition of a small amount of water (Table 1, entry 9). In contrast to phenylacetylene, methylpropiolate (**3b**) failed to give the corresponding oxazole, **4b**, with benzoyl chloride under gold catalysis (entry 12). The high stability of gold–propiolate complexes may be the reason for this failure,[24] so we also evaluated Cu^{I} salts, which are known to efficiently mediate ^{3}A couplings. CuBr·DMS efficiently catalyzed the formation of oxazole **4b** from methylpropiolate (entry 13), but it gave a lower yield than gold catalysis in the formation of **4a** from phenylacetylene (entry 10).

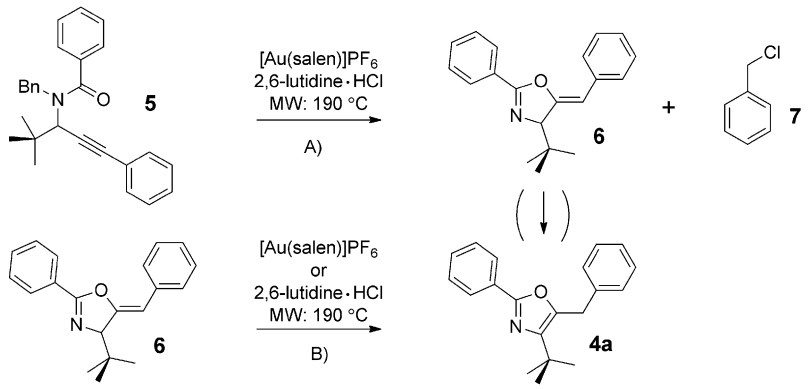
To probe the role(s) of the gold–salen complex in the catalytic cycle beyond the carbon–carbon bond-forming step, two control reactions were designed and the plausible intermediates **5** and **6** were synthesized (Figure 1, see the Supporting Information for details).[25] In the first reaction, the cyclization of propargyl amide **5** with various amounts of gold catalyst was studied (Figure 1A). The HCl salt of 2,6-lutidine was used as the proton source in these reactions because it is similar in pK_a value to the protonated imine that is the putative proton source under the regular reaction conditions. The formation of benzyl chloride (**7**), released in connection with the formation of oxazoline **6**, was used as a measure of the reaction progress because oxazoline **6** aromatizes into oxazole **4a**. The amount of **4a** plus **6** formed in the reaction correlates within 5% to the amount of **7** at all time points studied. In the second reaction, the isomerization of **6** into **4a** was studied with various amounts of gold or acid catalyst (Figure 1B).

Table 1. Optimization of the oxazole-forming reaction between *N*-benzylimine **1a**, acyl chloride **2a**, and alkynes **3a** and **b**.



Entry	R	Cat.	Cat. [mol%]	Solvent	*T* [°C]	Product	Yield [%][b]
1	Ph	$AuCl_3$	30	–	150	**4a**	49
2	Ph	$AuCl_3$	30	MeCN	190	**4a**	70
3	Ph	[Au(salen)]PF_6	20	–	150	**4a**	51
4	Ph	[Au(salen)]PF_6	20	MeCN	190	**4a**	83
5	Ph	[Au(salen)]PF_6	5	MeCN	190	**4a**	87
6	Ph	[Au(salen)]PF_6	5	MeCN	170	**4a**	89
7	Ph	[Au(salen)]PF_6	1	MeCN	190	**4a**	96
8	Ph	[Au(salen)]PF_6	1	MeCN	190	**4a**	80[c]
9	Ph	[Au(salen)]PF_6	1	MeCN	170	**4a**	91, 80[d]
10	Ph	CuBr·DMS	30	–	150	**4a**	41
11	Ph	CuCl	30	–	150	**4a**	44
12	CO_2Me	[Au(salen)]PF_6	5	MeCN	170	**4b**	0
13	CO_2Me	CuBr·DMS	30	–	150	**4b**	87[e]

[a] Reaction run on a 1.0 mmol scale (imine) with alkyne (2 equiv) and acyl chloride (1 equiv) for 15 min with microwave heating. DMS = Dimethylsulfide. [b] Measured by NMR spectroscopy with mesitylene as an internal standard. [c] 1.1 equivalents of alkyne were used. [d] Yield of isolated product. Reaction performed on a 2.4 g scale. [e] Yield of isolated product. [f] Thermal ellipsoid plot at 50% probability. Hydrogen atoms are omitted.



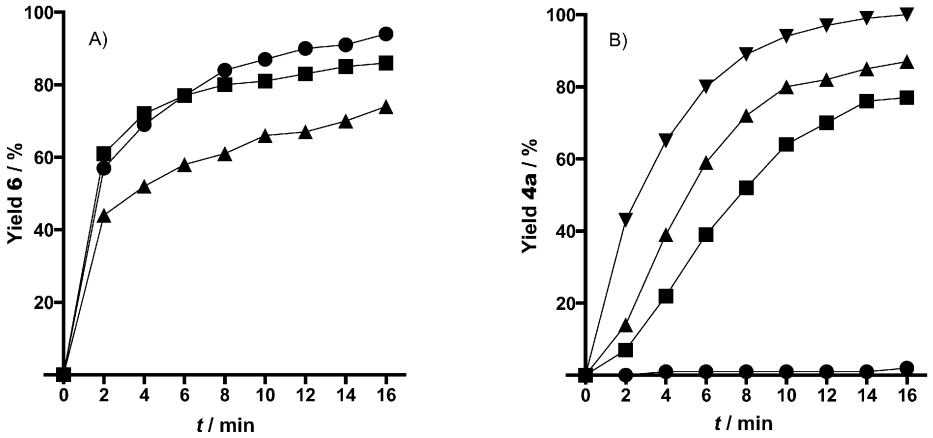
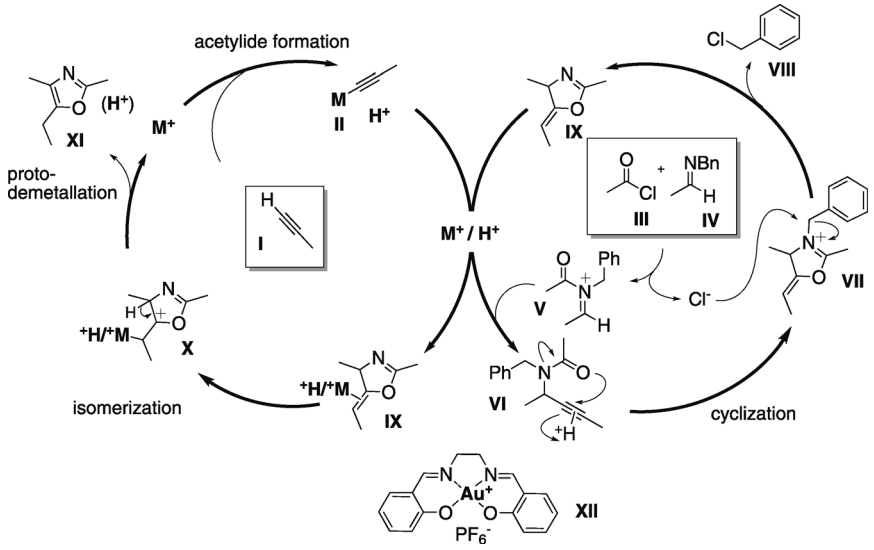


Figure 1. Kinetic data obtained by ^{1}H NMR spectroscopy for A) the cyclization of propargyl amide **5** into oxazoline **6** and B) the isomerization of oxazoline **6** into oxazole **4a** with various amounts of catalysts (●: no catalyst, ■: 5% [Au(salen)]PF_6, ▲: 10% [Au(salen)]PF_6, ▼: 5% 2,6-lutidine·HCl).

The following qualitative kinetic observations were made: 1) The cyclization to generate oxazoline **6** is similar in rate in the presence and absence of the gold catalyst. This observation is in line with the previous observation that Au^{III} does not catalyze cycloisomerization of propargyl alkynes substituted at the terminal alkyne position.[11e–g] The small rate differences observed in the formation of **6** can be attributed to a less efficient reaction (side-product formation) at higher catalyst concentrations, rather than a lower reaction rates. This is corroborated by the essentially full conversion of starting material **5** in all three experiments. 2) The thermal isomerization of the *exo* double bond of **6** to form **4a** is negligible under these conditions. With an increase in the gold-catalyst concentration, the isomerization proceeds faster. The isomerization of **6** into **4a** is, however, cleaner (less byproduct formation) with the lower gold-catalyst loading. With 10 mol% of 2,6-lutidine·HCl, the acid-catalyzed cyclization is fast and gives oxazole **4a** quantitatively within the allotted 16 min. A mixture of [Au(salen)]PF_6 and HCl·lutidine (5+5 mol%) was also tried for the isomerization of **6**. No significant nonlinear effect was observed in this experiment; the reaction rate was equivalent to that of the combined rates of the individual catalysts. These observations suggest that gold is not involved to an appreciable extent in facilitating the cyclization step but does contribute to the isomerization of **6** into **4a**, which led us to propose the mechanism outlined in Scheme 2: The oxazole-forming process is initiated by the addition of metal acetylide **II** to the activated *N*-acyl iminium salt **V** to give propargyl amide **VI**.[17] The proton released during alkyne activation then activates the triple bond of **VI** for attack of the amide oxygen atom. The benzyl group of the resulting iminium ion **VII** is released as benzyl chloride (**VIII**) by



Scheme 2. Proposed mechanism for the gold-catalyzed formation of oxazoles from *N*-benzylimines, acyl chlorides, and alkynes.

attack of a chloride ion originating from the initial acylation of imine **IV**. Finally, the isomerization of **IX** to produce oxazole **XI** is mediated by a combination of Brönsted acid and metal catalysis.[26]

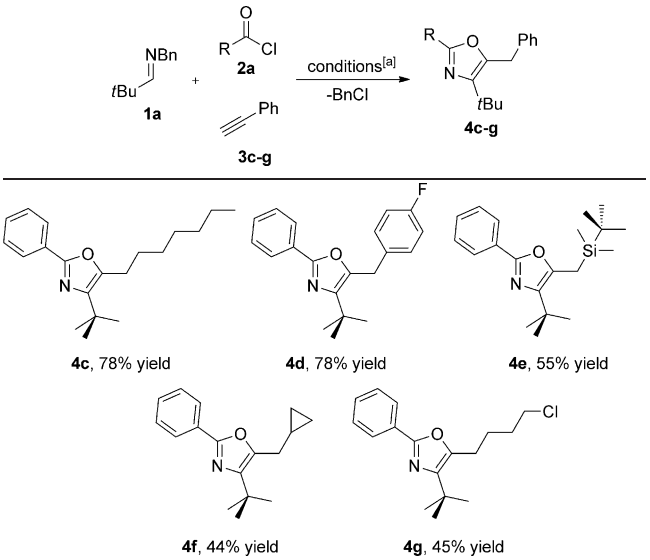
The scope of the reaction was investigated by varying the substrates corresponding to each position of the oxazole ring. The study was conducted with gold catalysis because the copper conditions are less general with respect to nonacceptor alkynes. A catalyst loading of 5 mol% was beneficial with most functionalized alkynes. Alkyl, aryl, and cyclopropyl-substituted alkynes all participate in the reaction to give the corresponding oxazole products in moderate to good yields (Table 2). Valuable handles for further derivatizations like alkyl chlorides and silyl groups are also readily incorporated at this position, as shown by the formation of **4g** and **4e**.

A variety of acid chlorides comprising aryl, heterocyclic, and aliphatic structures all provided the corresponding oxazoles in good to excellent yields (Table 3). Even the sterically encumbered pivaloyl chloride gave the corresponding bis-2,4-*tert*-butyl-substituted oxazole product **4j**, albeit at a lower yield.

With multifunctionalized reagents, the reaction can be used to assemble more than one heterocycle in a single operation. An illustrative example is the reaction with triacid chloride **2g** (Scheme 3). In this transformation, a total of seven components are assembled to form the final trioxazole **4m** through nine bond-forming events in 33% yield after isolation. This result is also interesting in light of the possible pincer-ligand properties of this compound.

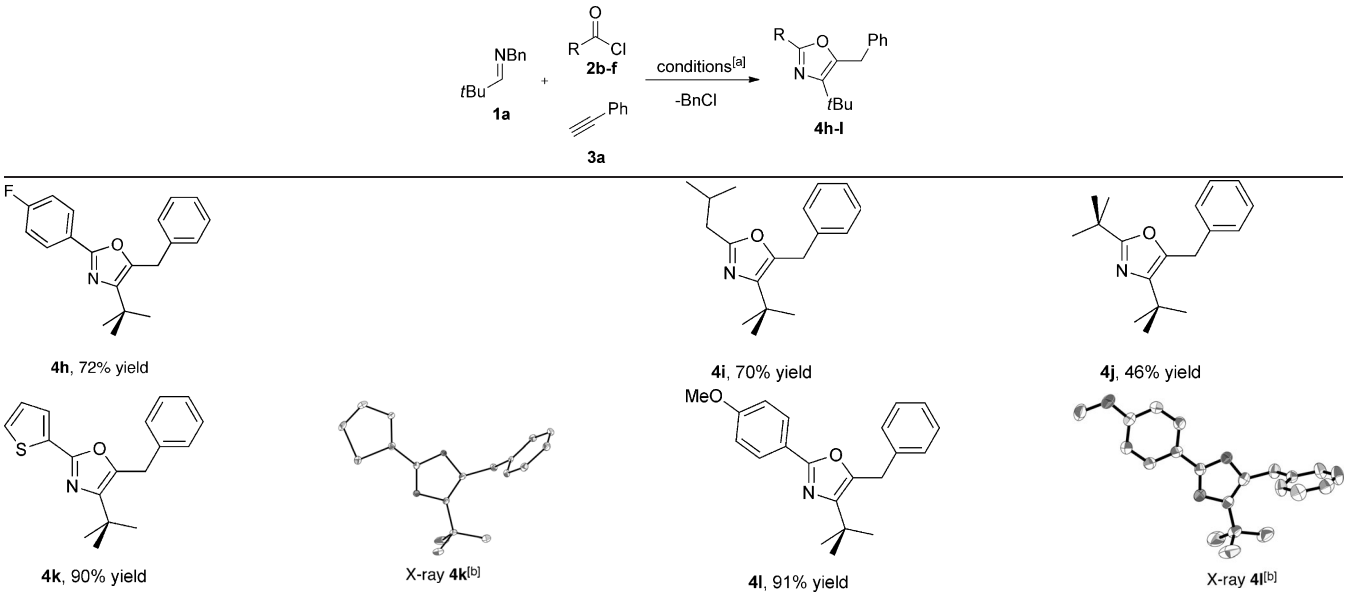
Various *N*-benzylimines with geminal substitution at the imine α-position can participate in the reaction. Substituents such as alkenes, ethers, and esters are compatible with this position (Table 4). In agreement with what would be expected from prior observations,[17] enolizable (that is, aliphatic) imines do not give oxazole formation. As is evident from the isolation of *N*-benzyl enamides in these experiments, this failure originates from the carbon–carbon bond-forming step in the alkyne–iminium coupling. Aryl imines give poor yields under gold catalysis. By using the Cu-catalyzed procedure, **4s** was isolated in 27% yield. Ethyl glyoxalate *N*-benzylimine gave a trace of product (4%; not shown). Interest-

Table 2. Oxazole formation with various alkynes.

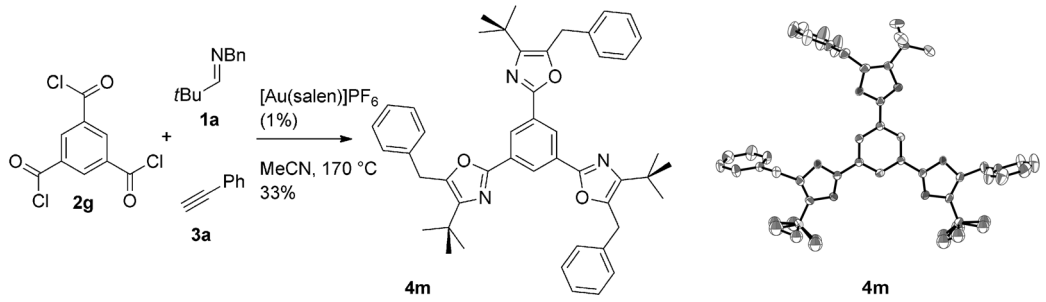


[a] Reaction run on a 0.5 mmol scale (imine) with alkyne (2 equiv), acyl chloride (1 equiv), and 5 mol% of [Au(salen)]PF_6 with microwave heating (170 °C).

Table 3. Oxazole formation with various acyl chlorides.

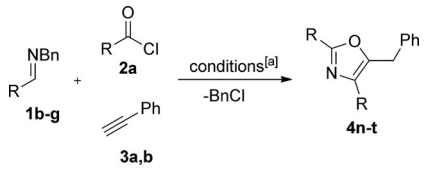


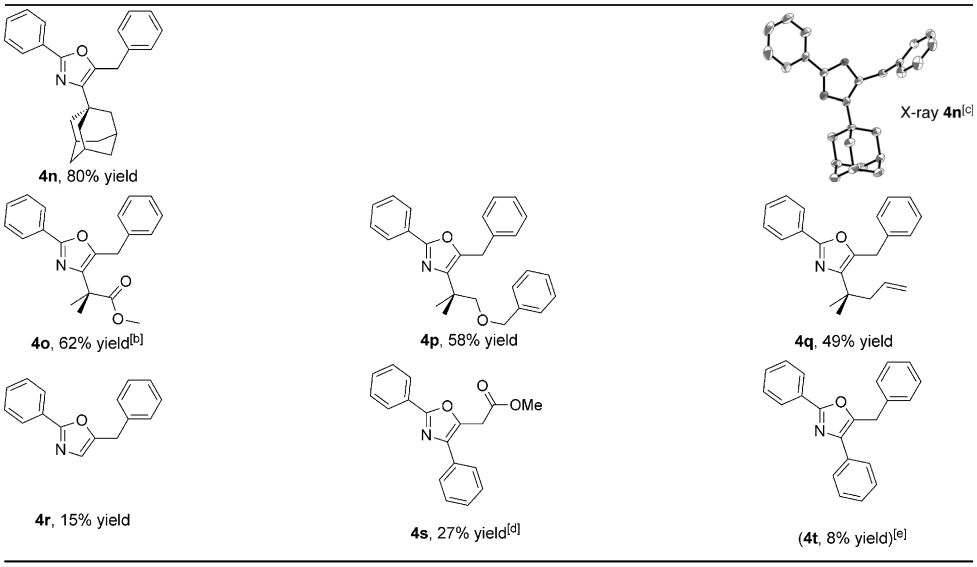
[a] Reaction run on a 0.5 mmol scale (imine) with alkyne (2 equiv), acyl chloride (1 equiv), and 1 mol% of [Au(salen)]PF_6 with microwave heating (170 °C). [b] Thermal ellipsoid plots at 50% probability. Hydrogen atoms are omitted.



Scheme 3. Left-hand side: seven-component reaction to form trioxazole **4m**. Right-hand side: the thermal ellipsoid plot at 50% probability and the rotational distortions on two of the *tert*-butyl groups. Hydrogen atoms are omitted.

Table 4. Oxazole formation with various *N*-benzylimines.



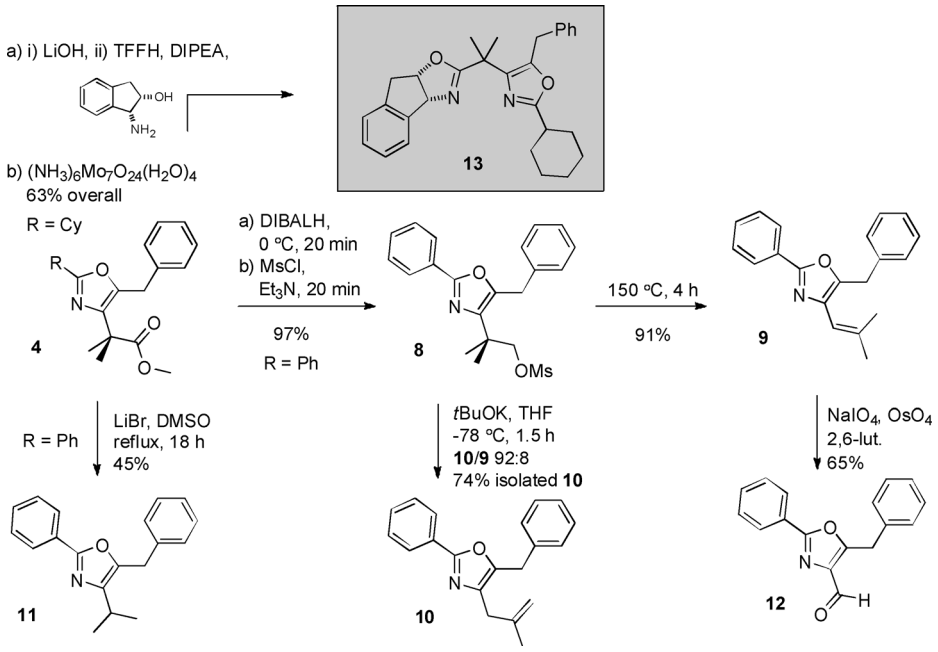


[a] Reaction run on a 0.5 mmol scale (imine) with alkyne (2 equiv), acyl chloride (1 equiv), and 1 mol% of [Au(salen)]PF_6 with microwave heating (170 °C, 15 min). [b] 5 mol% of [Au(salen)]PF_6 was used. [c] Thermal ellipsoid plot at 50% probability. Hydrogen atoms are omitted. [d] CuBr·DMS (20 mol%) was used as the catalyst. [e] Measured by NMR spectroscopy with mesitylene as an internal standard.

ingly, methylene *N*-benzylimine gave 15% of the corresponding 2,5-di-substituted oxazole **4r**. The majority of the material is lost as unspecific decomposition in the low yielding entries. The side reactions that account for the low yields with imines **1f–h** may be a result of the reduced steric bulk in the imine α-position relative to that of the corresponding trialkyl-substituted imines.

The synthetic utility of the reaction is highlighted by derivatization of the oxazole product. Ester hydrolysis followed by amide coupling[27] and a dehydrative cyclization[28] gives rapid access to a new class of chiral oxazoline–oxazole structures, exemplified by oxazole **13** (Scheme 4), with potential use as ligands in asymmetric catalysis.[29] Drawing from the design elements of related successful oxazoline systems,[30] the geminal dimethyl group that enabled efficient oxazole formation now conveniently serves to preorganize the bidentate structure for metal binding. The short and modular nature of this synthesis should be of value in developing ligand libraries.

With the aim of circumventing the limitation of quaternary substitution at the oxazole 4-position, we explored rearrangement reactions. Access to 4-vinyl oxazole **9** can be accomplished through a surprisingly efficient thermal 1,2-rearrangement of mesylate **8**, readily available from **4o** in two steps (Scheme 4).[31] Vinyl oxazoles like **9** are valuable as masked precursors to a range of functional structures, including 4-carboxy oxazoles, a motif prevalently found in bioactive molecules including natural products and pharmaceuticals. Rearrangement of **8** under kinetic conditions (*t*BuOK, −78 °C) gave 4-(2-methylpropenyl)oxazole **10**, with good selectivity (**10**/**9** = 92:8) and yield. Whereas similar rearrangements have been extensively studied with aryl migrating groups[32] and have been reported as side reactions for other heterocyclic migrating groups,[33] the rearrangements of mesylate **8** constitute rare and distinctively efficient examples of this type of reaction with an electron-rich heterocycle as the migrating entity. Finally, direct decarboxylation of **4o** under modified Krapcho conditions exemplifies a convenient entry to tertiary alkyl substitution at the oxazole 4-position.[34a] To the best of our knowledge, this is



Scheme 4. Application and post-MCR synthetic modifications of the oxazole products. DIBALH = diisobutylaluminum hydride; 2,6-lut. = 2,6-lutidine; TFFH = tetramethylfluoroformamidinium hexafluorophosphate.

the first example of a direct decarboxylation at this position of an oxazole structure.[34b]

Conclusion

An efficient gold-catalyzed multicomponent domino reaction to form oxazoles by the bridging of catalytic acetylide additions to imines and cycloisomerization of propargyl amides is presented. Trisubstituted oxazoles displaying a series of synthetically useful functional groups are formed in a single step in up to 96% yield. The use of a sacrificial benzyl group allows for product formation directly from readily available *N*-benzylimines and feedstock reagents like alkynes and acyl chlorides. The reaction also retains the efficiency on over a gram scale. The role of the gold catalyst was investigated, and in addition to catalyzing the carbon–carbon bond-forming step, gold was shown to mediate the isomerization of the intermediate oxazoline into the final aromatic system, but not the preceding cyclization step. Interestingly, the mechanism of the reaction would enable efficient oxazole formation also through nonterminal alkynes. The reaction was showcased in a highly modular and short assembly of a new type of chiral oxazoline–oxazole structure with potential use as a nitrogen–nitrogen bidentate ligand in asymmetric catalysis. The synthetic utility of the title reaction to provide access to oxazole products beyond structures with a geminal dialkyl moiety at the oxazole 4-position is highlighted through efficient 1,2-migration reactions to give vinyl- and allyl-substituted oxazoles, respectively. A decarboxylation reaction was shown to provide a dialkyl substituent at the same position. Further studies of this reaction and extensions to related systems are underway.

Experimental Section

Representative procedure: A microwave vial was charged with [Au(salen)]PF_6 (3.04 mg, 5.00 μmol, 1 mol%) and flushed with nitrogen. The catalyst was dissolved in anhydrous CH_3CN (0.25 mL), and imine **1a** (103 μL, 0.50 mmol, 1.0 equiv), phenylacetylene (110 μL, 1.00 mmol, 2.0 equiv), and 2-thiophenecarbonyl chloride (53 μL, 0.50 mmol, 1.0 equiv) were added sequentially. The resulting mixture was heated by microwave irradiation, with a ceiling temperature of 170 °C and the sample absorption set to "very high" for 15 min. The crude reaction mixture was dissolved in CH_2Cl_2 and a small amount of silica was added to the mixture. The resulting slurry was concentrated under reduced pressure. The concentrate was added to a silica gel column and eluted with CH_2Cl_2/heptane (1:3). The product-containing fractions were pooled and concentrated under reduced pressure to give oxazole **4k** (137 mg, 92%) as orange crystals.

Acknowledgements

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[1] S. Reck, W. Friedrichsen, *J. Org. Chem.* **1998**, *63*, 7680–7686.
[2] R. Y. Tsien, R. T. J. Rink, M. Poenie, *Cell Calcium* **1985**, *6*, 145–157.
[3] A. Plant, F. Stieber, J. Scherkenbeck, P. Losel, H. Dyker, *Org. Lett.* **2001**, *3*, 3427–3430.
[4] R. Hirohashi, Y. Hishiki, S. Ishikawa, *Polymer* **1970**, *11*, 297–308.
[5] V. S. C. Yeh, *Tetrahedron* **2004**, *60*, 11995–12042.
[6] D. C. Palmer, S. Venkatraman in *The Chemistry of Heterocyclic Compounds: A Series of Monographs. Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A* (Ed.: D. C. Palmer), John Wiley & Sons, Hoboken, NJ, **2003**.
[7] a) B. Kunze, R. Jansen, G. Hofle, H. Reichenbach, *J. Antibiot.* **2004**, *57*, 151–155; b) S. Essig, S. Bretzke, R. Müller, D. Menche, *J. Am. Chem. Soc.* **2012**, *134*, 19362–19365.
[8] L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, John Wiley & Sons, Hoboken, NJ, **2010**.
[9] For reviews, see: a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115–2134; b) F. W. Hartner in *Comprehensive Heterocyclic Chemistry II, Vol. 3* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, UK, **1996**, pp. 262–318, and references therein.
[10] For recent examples, see: a) D. Bonne, J. Zhu, M. Dekhane, *Angew. Chem.* **2007**, *119*, 2537–2540; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485–2488; b) C. Lalli, M. J. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.* **2011**, *17*, 880–889; c) I. Cano, E. Alvarez, M. C. Nicasio, P. J.

Pérez, *J. Am. Chem. Soc.* **2011**, *133*, 191–193; d) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem.* **2011**, *123*, 9093–9097; *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935; e) C. L. Zhong, B. Y. Tang, P. Yin, Y. Chen, L. He, *J. Org. Chem.* **2012**, *77*, 4271–4277, and references therein.

[11] For representative examples, see: a) P.-Y. Coqueron, C. Didier, M. A. Ciufolini, *Angew. Chem.* **2003**, *115*, 1451–1454; *Angew. Chem. Int. Ed.* **2003**, *42*, 1411–1414; b) A. Bacchi, M. Costa, B. Gabriele, G. Pelizzi, G. Salerno, *J. Org. Chem.* **2002**, *67*, 4450–4457; c) E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocornola, *J. Org. Chem.* **2008**, *73*, 4746–4749; d) A. Saito, K. Limura, Y. Hanzawa, *Tetrahedron Lett.* **2010**, *51*, 1471–1474; e) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394; f) S. Doherty, J. G. Knight, A. S. K. Hashmi, C. H. Smyth, N. A. B. Ward, K. J. Robson, S. Tweedley, R. W. Harrington, W. Clegg, *Organometallics* **2010**, *29*, 4139–4147; g) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963; h) A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Romninger, *Eur. J. Org. Chem.* **2011**, 4595–4602; i) G. Bartoli, C. Cimarelli, R. Cipolletti, S. Diomedi, R. Giovannini, M. Mari, L. Marsili, E. Marcantoni, *Eur. J. Org. Chem.* **2012**, 630–636; j) A. Saito, A. Matsumoto, Y. Hanzawa, *Tetrahedron Lett.* **2010**, *51*, 2247–2250; k) X. Zhang, W. T. Teo, P. W. H. Chan, *J. Organomet. Chem.* **2011**, *696*, 331–337; l) Y.-m. Pan, F.-j. Zheng, X.-h. Lin, Z.-p. Zhan, *J. Org. Chem.* **2009**, *74*, 3148–3151.

[12] For representative examples, see: a) C. Wan, L. Gao, Q. Wang, J. Zhang, Z. Wang, *Org. Lett.* **2010**, *12*, 3902–3905; b) H. Jiang, H. Huang, H. Cao, C. Qi, *Org. Lett.* **2010**, *12*, 5561–5563; c) W. He, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485; d) H. Jiang, X. Wei, L. Huang, H. Chen, W. Wu, H. Huang, *Chem. Sci.* **2012**, *3*, 3022.

[13] For a recent review on modern oxazole-forming reactions, see: A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, DOI: 10.1021/cr300333u.

[14] For a recent review, see: *Topics in Heterocyclic Chemistry: Synthesis of Heterocycles via Multicomponent Reactions, Vol. 1* (Eds.: R. V. A. Orru, E. Ruijter), Springer-Verlag, Berlin, **2010**.

[15] For representative examples, see: a) B. Wu, J. Wen, J. Zhang, J. Li, Y.-Z. Xiang, X.-Q. Yu, *Synlett* **2009**, 500–504; b) E. Merkul, O. Grotkopp, T. J. J. Müller, *Synthesis* **2009**, 502–507; c) D. A. Black, B. A. Arndtsen, *Tetrahedron* **2005**, *61*, 11317–11321; d) M. Tran-Dubé, S. Johnson, I. McAlpine, *Tetrahedron Lett.* **2013**, *54*, 259–261; e) M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* **2004**, 2712–2713.

[16] For recent examples, see: a) A. B. Dyatkin, R. A. Rivero, *Tetrahedron Lett.* **1998**, *39*, 3647–3650; b) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473–4475; c) E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, *Tetrahedron Lett.* **2007**, *48*, 7184–7190; d) P. Li, Y. Zhang, L. Wang, *Chem. Eur. J.* **2009**, *15*, 2045–2049; e) Y. Zhang, P. Li, M. Wang, L. Wang, *J. Org. Chem.* **2009**, *74*, 4364–4367; f) C. Fischer, E. M. Carreira, *Synthesis* **2004**, 1497–1503; g) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585.

[17] D. A. Black, B. A. Arndtsen, *Org. Lett.* **2004**, *6*, 1107–1110.

[18] For examples of ^{3}A coupling–cycloisomerization reactions, see: a) H. Z. S. Syeda Huma, R. Halder, S. S. Karla, J. Das, J. Iqbal, *Tetrahedron Lett.* **2002**, *43*, 6485–6488; b) N. Sakai, N. Uchida, T. Konakahara, *Tetrahedron Lett.* **2008**, *49*, 3437–3440; c) D. Chernyak, N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2010**, *352*, 961–966; d) W.-J. Yoo, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 1503–1506; e) N. Chernyak, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2803–2806; *Angew. Chem. Int. Ed.* **2010**, *49*, 2743–2746; f) Q. Zhang, M. Chang, X. Y. Hu, B. G. Li, J. X. Ji, *J. Am. Chem. Soc.* **2010**, *132*, 7256–7257; g) N. T. Patil, V. S. Raut, *J. Org. Chem.* **2010**, *75*, 6961–6964; h) B. Yan, Y. Liu, *Org. Lett.* **2007**, *9*, 4323–4326.

[19] C. Jorand-Lebrun, D. Valognes, S. Halazy, *Synth. Commun.* **1998**, *28*, 1189–1195.

[20] M. J. Campbell, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1369–1378.

[21] V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*, 1529–1532.

[22] A control experiment to probe for the possibility of Friedel–Craft side reactions was carried out. Oxazole **4a** and benzyl chloride were subjected to $AuCl_3$ or $[Au(salen)]PF_6$ under otherwise standard conditions. No reaction was observed by ^{1}H NMR spectroscopy or MS in this experiment, and the starting materials were recovered.

[23] D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246.

[24] G. F. Manbeck, M. C. Kohler, M. R. Porter, R. A. Stockland, Jr., *Dalton Trans.* **2011**, *40*, 12595–12606.

[25] A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241.

[26] We cannot exclude the possibility that an acid or gold species originating from thermal decomposition of the catalyst catalyzes the isomerization.

[27] M. Pittelkow, F. S. Kamounah, U. Boas, B. Pedersen, J. B. Christensen, *Synthesis* **2004**, 2485–2492.

[28] A. Sakakura, R. Kondo, K. Ishihara, *Org. Lett.* **2005**, *7*, 1971–1974.

[29] For pioneering work on nitrogen–nitrogen bidentate oxazoline ligands, see: a) H. Brunner, R. Becker, G. Riepl, *Organometallics* **1984**, *3*, 1354–1359; b) H. Brunner, U. Obermann, P. Wimmer, *Organometallics* **1989**, *8*, 821–826.

[30] For reviews on oxazoline ligands, see: a) M. Gómez, G. Muller, M. Rocamora, *Coord. Chem. Rev.* **1999**, *769*, 193–195; b) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[31] For a review of 1,2-rearrangements, see: J. R. Hanson in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Vol. 3* (Ed.: G. Pattenden), Pergamon, Oxford, UK, **1991**, 705–719.

[32] For representative early examples, see: a) E. S. Wallis, P. I. Bowman, *J. Org. Chem.* **1936**, *1*, 383–392; b) H. E. Zimmerman, F. J. Smentowski, *J. Am. Chem. Soc.* **1957**, *79*, 5455–5457.

[33] For examples of rearrangements with migrating heterocycles, see: P. Korakas, S. Chaffee, J. B. Shotwell, P. Duque, J. L. Wood, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12054–12057; R. Ritchie, J. E. Saxton, *J. Chem. Res. Synop.* **1990**, 48–49.

[34] For a recent review on Krapcho decarboxylations, see: a) P. S. Poon, A. K. Banerjee, M. S. Laya, *J. Chem. Res.* **2011**, *35*, 67–73; for decarboxylation in the oxazole 2-position, see: b) N. A. Meanwell, M. J. Rosenfeld, J. J. K. Wright, C. L. Brassard, J. O. Buchanan, M. E. Federici, J. S. Fleming, M. Gamberdella, K. S. Hartl, G. B. Zavoico, S. M. Seiler, *J. Med. Chem.* **1993**, *36*, 3871–3883.

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Multicomponent Reactions

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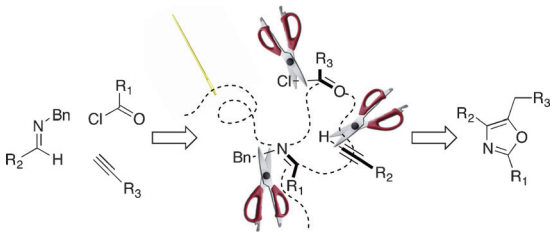
Catalytic Three-Component Domino Reaction for the Preparation of Trisubstituted Oxazoles



Crossing bridges: Oxazoles are generated in up to 96% yield from readily available imines, acid chlorides, and alkynes by using a gold(III) catalyst (see scheme). The use of a sacrificial benzyl group enables the bridging of an imine–alkyne coupling and a cycloisomerization manifold to form the oxazole products in a single domino reaction.