Organic LETTERS

Letter

pubs.acs.org/OrgLett

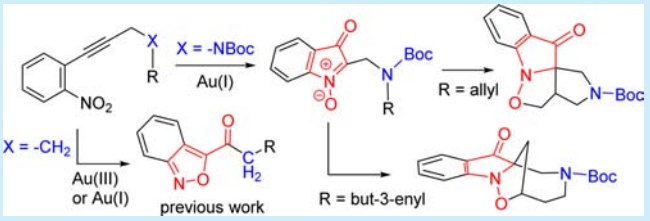
Tuning the Regioselectivity of Gold-Catalyzed Internal Nitroalkyne Redox: A Cycloisomerization and [3 + 2]-Cycloaddition Cascade for the Construction of *spiro*-Pseudoindoxyl Skeleton

Chepuri V. Suneel Kumar and Chepuri V. Ramana*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. HomiBhabha Road, Pune 411 008, India

Supporting Information

ABSTRACT: A simple domino process for the construction of the tricyclic core present in the *spiro*-pseudoindoxyl natural products has been developed. This involves two intramolecular events: the Au-catalyzed nitroalkyne redox leading to isatogen and its subsequent [3 + 2]-cycloaddition with a suitably positioned olefin. The option to modulate the size of the *spiro*-annulated ring, which is an important variable in this class of natural products, has been explored. Overall, this process molds a linear precursor into a tricyclic system with complete step, atom, and redox economy.

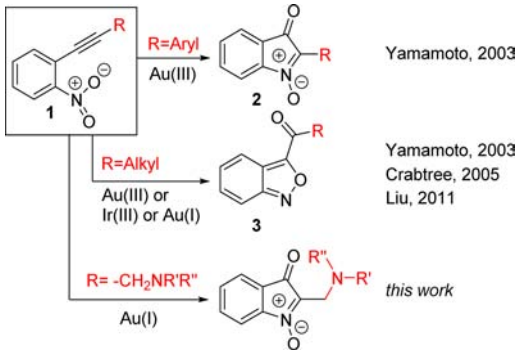


The substrate(s) engineering and sequential maneuver of diverse reactions in a single pot plays a central role in the construction of a multitude of diverse molecules.[1] When metal complexes are employed as catalysts for such cascade transformations, these processes are highly step and eco-efficient.[2,3] In recent years, gold complexes have been found to be more prominent in this area by virtue of their remarkable reactivity in catalyzing distinct and unusual organic transformations.[4] A particularly interesting class of gold-catalyzed reactions is the catalytic internal redox cyclization.[5] The gold-catalyzed oxygen atom transfer to alkynes is a well-known addition−elimination process employing nucleophilic oxygen atom donors such as nitro,[6] amine-/pyridine *N*-oxides,[7] nitrone,[8] sulfoxides,[9] and epoxides[10] on the activated alkynes. The cyclization of *o*-(arylalkynyl)nitrobenzenes reported by Yamamoto and co-workers was one of the early examples for the gold(III)-catalyzed nitro-alkyne redox process that has provided a practical alternative for the synthesis of 2-aryl-3-oxo-3*H*-indole 1-oxide unit (trivially known as isatogens) and has been attempted later with Ir and Pd complexes (Scheme 1).[6a−c]

An elegant combination of the internal nitroalkyne redox of 1-ethynyl-2-nitrobenzenes and the subsequent intermolecular cycloaddition has been revealed by Liu and co-workers by employing Au[I]-complexes.[6d] However, with the internal alkynes, when the pendant alkyne substituent is an alkyl group, benzo[*c*]isoxazole (trivially known as anthranil) was formed exclusively with either of the Au[I/III] or even with [Ir] complexes.[6]

These alkyne-substituent-dependent complementary product formations in these gold-catalyzed nitroalkyne cycloisomerization resulted primarily from the competing 6-*endo* mode of cyclization over 5-*exo* because of the +I nature of the pendant alkyl group on the alkyne. Keeping in mind the previous information on how the electronic factors influence the regioselectivity of the alkynol cycloisomerization,[11] we

Scheme 1. Regioselectivity Issues in the Au-Catalyzed Nitroalkyne Cycloisomerization



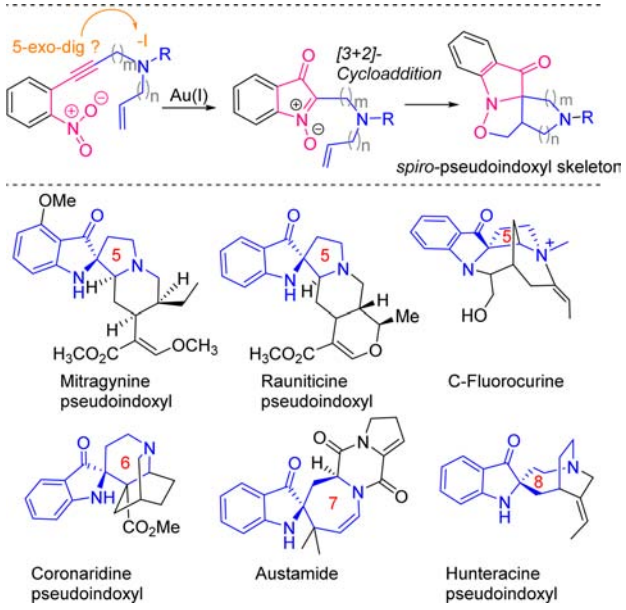
hypothesized that the presence of an electron-withdrawing group such as nitrogen on a pendant chain should promote the 5-*exo* mode of cyclization inter alia isatogen formation.[12] When the pendant group carries a suitably positioned olefin unit, the subsequent intramolecular [3 + 2]-cycloaddition should lead to the tricyclic *spiro*-pseudoindoxyl skeleton (Scheme 2).[13]

The *spiro*-pseudoindoxyl skeleton is a rare but important structural unit present in the indole class of alkaloids (Scheme 2).[14] A biomimetic approach involving the oxidative rearrangement of the corresponding fused indole−alkaloid is generally employed in the synthesis of this class of natural products.[15] There are very few reports for the synthesis of the central tricyclic core employing the nonoxidative methods.[16−18] The intramolecular attack of an enolate on an arylazide (Smalley cyclization) is one of the early examples reported in this area.[16] Recently, Sorensen's group has developed a simple interrupted

Received: July 27, 2014
Published: August 28, 2014

dx.doi.org/10.1021/ol502213w | *Org. Lett.* 2014, 16, 4766−4769

Scheme 2. *spiro*-Pseudoindoxyl Skeleton Construction via Nitroalkyne Cycloisomerization and Subsequent [3 + 2]-Cycloaddition



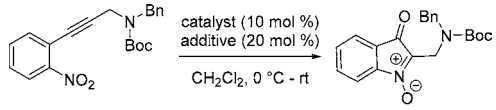
Ugi method for this core in dealing with their total synthesis of 11-methoxymitragynine pseudoindoxyl.[18] As shown in Scheme 2, apart from their topological complexity, the structural diversity of the annulated ring in these *spiro*-pseudoindoxyl natural products (the nature and the size) is one of the important challenges in their synthesis, and a general approach addressing these issues is well sought. As given in Scheme 2, our working hypothesis is founded upon the cyclization of *o*-(arylalkynyl)nitrobenzenes leading to the isatogen and its subsequent intramolecular [3 + 2]-cycloaddition with a suitably placed olefin.[19]

Our first concern in this program was the challenging 5-*exo* vs 6-*endo* nitroalkyne cycloisomerization with Au complexes and the viability of the above hypothesis. As a first step in this direction, the cyclization of Boc-protected propargyl amine **1aa-Boc** has been examined with different gold catalysts. Gratifyingly, as given in Table 1, with the majority of the Au complexes examined, the isatogen formation was the major pathway, with variations mainly in the isolated yields. The best results in terms of the yields and time were obtained with the $AuCl(PPh_3)$ in combination with $AgSbF_6$. Even with $AuBr_3$, isatogen **2aa-Boc** was the main product; however, the reaction yield was moderate. The reactions with $AuCl(PMe_3)$ and $AuCl(BiPh^tBu_2P)$ required longer times. On the other hand, the combination of $AuCl(PPh_3)$ with other silver salts like $AgBF_4$ and $AgNTf_2$ resulted in complete conversion of the starting material with good to excellent yields. However, the combination of $AuCl(PPh_3)$ with AgOTf, AgOAc, and $AgOCOCF_3$ resulted in the high recovery of the starting material. In contrast, $AgCO_3$ and $AgNO_3$ combinations are completely ineffective for this transformation. The scope of this reaction has been generalized by employing various nitroalkynes, especially by varying (i) the amine protecting group and (ii) the substituents on the aromatic as well as on the amine unit.

As shown in Scheme 3, with the majority of the propargylamines having *N*-Boc or *N*-Ac groups, the isatogen formation was the major event. However, with both *N*-Ms and *N*-Ts derivatives, the starting compounds were found to be intact. The nature of the substituents on the nitroaryl ring seems to substantially influence the outcome of the reaction. The reactions with the substrates having electron-donating groups like MeO− and Me− are smooth, and the yields are good. However, with substrates having a −Cl group on the aryl ring, the participation of the *N*-Boc group in a 6-*endo-dig* fashion leading to cyclic carbamate **4ca** was found to be the main event. Nonetheless, replacing the −Boc with −Ac in these cases led to the corresponding isatogens exclusively.

With the variation of N-substituents, various *N*-aryl derivatives, as well as cyclic lactams, were found to be compatible under these conditions and exclusively provided the isatogens in the majority of the cases. However, when the

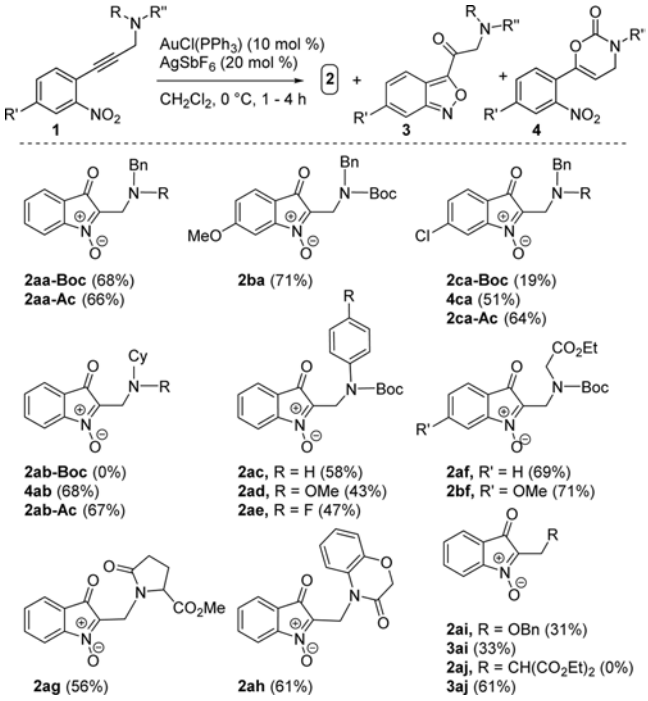
Table 1. Optimization of the Reaction with Au Combinations



entry	catalyst	additive	time (h)	yield[a] (%)
1	$AuBr_3$		3	44
2	$AuCl(PMe_3)$	$AgSbF_6$	3	47
3	**$AuCl(PPh_3)$**	**$AgSbF_6$**	**2**	**68**
4	$AuCl(BiPh^tBu_2P)$	$AgSbF_6$	4	10
5[b]	$AuCl(PPh_3)$	AgOTf	7	22
6	**$AuCl(PPh_3)$**	**$AgNTf_2$**	**3**	**60**
7	**$AuCl(PPh_3)$**	**$AgBF_4$**	**3**	**62**
8[b]	$AuCl(PPh_3)$	$AgOCOCF_3$	24	25
9[b]	$AuCl(PPh_3)$	AgOAc	24	18
10	$AuCl(PPh_3)$	$AgNO_3$	48	NR
11	$AuCl(PPh_3)$	$AgCO_3$	48	NR

[a]Isolated yields. [b]Yield with respect to the recovered starting material; NR = no reaction.

Scheme 3. Scope of the Au-Catalyzed Isatogen Synthesis

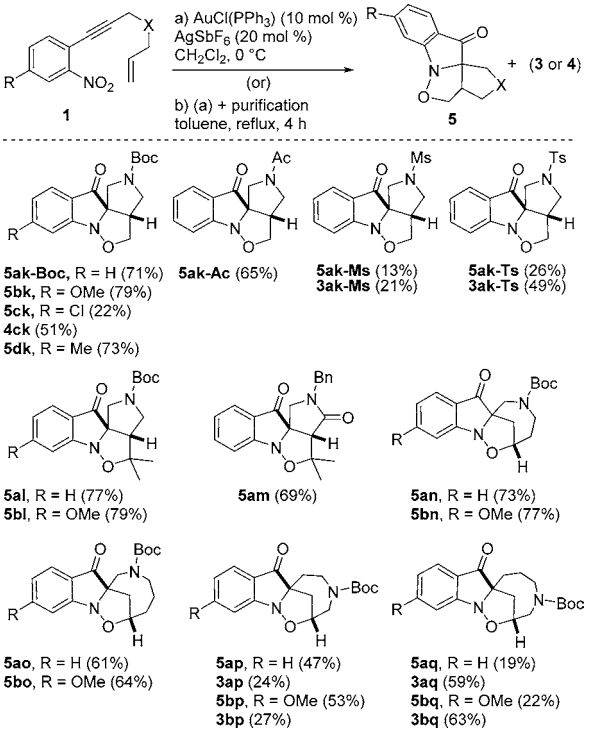


dx.doi.org/10.1021/ol502213w | *Org. Lett.* 2014, 16, 4766−4769

nitrogen is having a bulky cycloalkyl group, the cyclic carbamate formation was found to be the main event. Once again, replacing the −Boc with −Ac gave the corresponding isatogen. This complementary alkyne functionalization is quite interesting and reveals how the subtle electronic perturbations on the aryl ring or the steric crowding around the nitrogen will switch the reacting nucleophiles present. In regard to the *N*-propargylaniline substrates **1ac**−**ae**, the cyclization of the simple unsubstituted aniline derivative **1ac** proceeded smoothly and provided the isatogen **2ac** in moderate yield. On the other hand, the reactions with **1ad** and **1ae** are sluggish, and the corresponding isatogens **2ad** and **2ae** are obtained in poor yields. As a control, the cyclization of nitroalkynes **1ai** and **1aj** derived, respectively, from benzylpropargyl ether and propargylmalonate derivatives has been examined under similar conditions. In the case of the benzyl ether derivative **1ai**, a ∼1:1 mixture of isatogen **2ai** and anthranil **3ai** has been obtained. On the other hand, the cyclization of the propargylmalonate **1aj** gave exclusively the corresponding anthranil **3aj**. Overall, these results clearly indicate that the mode of cyclization is dependent upon the presence/absence of a heteroatom at the propargylic position and the magnitude of the −I effect that it can insert and also on the substituents present on the aryl ring as well as on the nitrogen.

Having successfully demonstrated our hypothesis on Au-catalyzed isatogen preparation via nitroalkyne cycloisomerziation, we next proceeded with examining the cycloisomerization−cycloaddition cascade leading to the tricyclic core of C2-*spiro*-pseudoindoxyl natural products. As shown in Scheme 4, the treatment of simple *o*-nitroenynamide **1ak-Boc** with the gold complex at 0 °C for 4 h gave exclusively the isoxazolidine **5ak-Boc** in 71% yield. Elaboration of this method involved the synthesis of various 3-(2-nitrophenyl)prop-2-yn-1-amine derivatives bearing different pendant *N*-alkenyl groups and varying the substituents on the alkene, the aromatic ring, as well as the protecting groups on the nitrogen (see the Supporting Information for the substrate synthesis). Scheme 4 reveals the scope of the current reaction with these substrates. As observed previously, with the majority of the propagylamine derivatives, the cycloisomerziation−cycloaddition cascade proceeded smoothly and provided exclusively the requisite isoxazolidine derivatives. Quite interestingly, even with the *N*-Ms and *N*-Ts derivatives **1ak-Ms** and **1ak-Ts**, the cycloisomerziation was facile; however, the anthranil formation was predominant over the isatogen (that subsequently underwent cycloaddition). As expected, the presence of the substituents like MeO− and Me− on the aryl ring gave the best results. On the other hand, the presence of a −Cl group on the aryl ring reduced the rate of the reaction and the cyclic carbamate was obtained as the major product.

Scheme 4. Au-Catalyzed Synthesis of *spiro*-Pseudoindoxyl Skeleton



Next, the scope of this reaction in the synthesis of higher anellated ring systems has been examined by employing *o*-nitroenynamide substrates **1an**−**aq** (see the Supporting Information for details) having the alkyne and alkene groups positioned at varying lengths from the central nitrogen. Surprisingly, with the propargyl-*N*-butenyl derivative, the cycloaddition was completely *endo*-selective resulting in the formation of a [4,2,1]-bridged bicylic product with the net annulation of a 7-membered heterocyclic ring.[20] This was even the case with the propargyl-*N*-pentenyl derivative **1ao**. However, in this case, the cycloaddition is not instantaneous. The intermediate isatogen needs to be isolated and then subjected for the cycloaddition in refluxing toluene. Coming to the substrate **1ap** (the positional isomers of **1an**) where the nitrogen has been moved two carbons away from the alkyne terminus, although the cycloisomerziation was not selective, the cycloaddition of the intermediate isatogen was spontaneous and gave the corresponding anthranil **3ap** and the bridged *spiro*-pseudoindoxyl derivative **5ap** in 24% and 47% yields, respectively. As expected, the selectivity dropped further when the number of linking carbons between the nitrogen and the alkyne terminus was increased to three (**1aq**). Like with the positional isomer **1ao**, in this case also, the cycloaddition has to be carried out separately and at elevated temperatures.

In summary, a simple approach for the construction of the complex *spiro*-indoxyl core present in a variety of pseudoindoxyl natural products has been developed. In this process, we have revealed some preliminary, yet important, observations on how to control the regioselectivity of internal nitroalkyne redox by employing the appropriate substituents at appropriate positions. To this end, this Au-catalyzed nitroalkyne cycloisomerization leading to isatogens has been combined with the intramolecular [3 + 2]-cycloaddition in a cascade fashion to arrive at the complex tetracyclic [6.5.*n*.5] frameworks in moderate to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vr.chepuri@ncl.res.in.

dx.doi.org/10.1021/ol502213w | *Org. Lett.* 2014, 16, 4766−4769

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.V.R. and C.V.S. thank CSIR (India) for funding this project (12 FYP ORIGIN program, CSC0108) and for a fellowship to C.V.S.

■ REFERENCES

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131−163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

(2) (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16. (b) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Top. Organomet. Chem.* **2006**, 259−294.

(3) (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259−281. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010−3021.

(4) Selected reviews on Au-catalysis: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239. (b) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65. (c) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387−391. (d) Hashmi, A. S. K.; Hutchings, G. J. *Angew.Chem. Int. Ed.* **2006**, *45*, 7896−7936. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (h) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351−3378.

(5) Selecteed reviews on gold-catalyzed internal redox processes: (a) Xiao, J.; Li, X. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226−7236. (b) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462−1479. (c) Zhang, L. M. *Acc. Chem. Res.* **2014**, *47*, 877−888. (d) Yeom, H. S.; Shin, S. *Acc. Chem. Res.* **2014**, *47*, 966−977.

(6) (a) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675−5677. (b) Li, X. W.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066−3073. (c) Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B. C.; Degterev, A. *Eur. J. Org. Chem.* **2010**, 5955−5966. (d) Jadhav, A. M.; Bhunia, S.; Liao, H. Y.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, *133*, 1769−1771.

(7) (a) Cui, L.; Peng, Y.; Zhang, L. M. *J. Am. Chem. Soc.* **2009**, *131*, 8394−8395. (b) Ye, L. W.; Cui, L.; Zhang, G. Z.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 3258−3259. (c) Ye, L. W.; He, W. M.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 8550−8551. (d) Lauterbach, T.; Gatzweiler, S.; Nosel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, *355*, 2481−2487. (e) Nosel, P.; Comprido, L. N. D.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **2013**, *135*, 15662−15666.

(8) (a) Yeom, H. S.; Lee, J. E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040−7043. (b) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. *Org. Biomol.Chem.* **2009**, *7*, 4744−4752. (c) Pati, K.; Liu, R. S. *Chem. Commun.* **2009**, 5233−5235. (d) Chen, D.; Song, G. Y.; Jia, A. Q.; Li, X. W. *J. Org. Chem.* **2011**, *76*, 8488−8494.

(9) (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160−4161. (b) Li, G. T.; Zhang, L. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156−5159. (c) Fang, R.; Yang, L. Z. *Organometallics* **2012**, *31*, 3043−3055. (d) Lu, B.; Li, Y. X.; Wang, Y. L.; Aue, D. H.; Luo, Y. D.; Zhang, L. M. *J. Am. Chem. Soc.* **2013**, *135*, 8512−8524.

(10) (a) Hashmi, A. S. K.; Bührle, M.; Salathé, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059−2064. (b) Lin, G. Y.; Li, C. W.; Hung, S. H.; Liu, R. S. *Org. Lett.* **2008**, *10*, 5059−5062.

(11) Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219−233.

(12) Selectivity switch in gold catalysis: (a) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855−2875. (b) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzic, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5848−5852. (c) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 1517−1528. (d) Hashmi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. *J. Org. Chem.* **2012**, *77*, 7761−7767.

(13) For gold catalysis followed by pericyclic reactions see: (a) Hashmi, A. S. K.; Jaimes, M. C. B.; Schuster, A. M.; Rominger, F. *J. Org. Chem.* **2012**, *77*, 6394−6408. (b) Hashmi, A. S. K.; Littmann, A. *Chem.—Asian J.* **2012**, *7*, 1435−1442.

(14) (a) Takayama, H.; Kurihara, M.; Subhadhirasakul, S.; Kitajima, M.; Aimi, N.; Sakai, S. *Heterocycles* **1996**, *42*, 87−92. (b) Borschberg, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1465−1491.

(15) (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871−3877. (b) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786−6788. (c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904−7905.

(16) (a) Ardakani, M. A.; Smalley, R. K. *Tetrahedron Lett.* **1979**, 4769−4772. (b) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724−6725. (c) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109−9122.

(17) (a) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504−5510. (b) Zhang, Y. Q.; Zhu, D. Y.; Jiao, Z. W.; Li, B. S.; Zhang, F. M.; Tu, Y. Q.; Bi, Z. G. *Org. Lett.* **2011**, *13*, 3458−3461.

(18) (a) Schneekloth, J. S.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096−3101. (b) Kim, J.; Schneekloth, J. S.; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849−2852.

(19) Selected reviews/papers on intramolecular nitrone cycloadditions: (a) Martin, J. N.; Jones, R. C. F. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: Hoboken, NJ, 2003; pp 1−81. (b) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298−326. (c) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497−3509. (d) Lebel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363−3368. (e) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900−4901. (f) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113−5123. (g) Smith, C. J.; Holmes, A. B.; Press, N. J. *Chem. Commun.* **2002**, 1214−1215.

(20) (a) Bhattacharjya, A.; Chattopadhyay, P.; McPhail, A. T.; McPhail, D. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1508−1509. (b) Shing, T. K. M.; Fung, W. C.; Wong, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 449−450. (c) Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **1999**, *55*, 12157−12174. (d) Krenske, E. H.; Agopcan, S.; Ayiyente, V.; Houk, K. N.; Johnson, B. A.; Holmes, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 12010−12015.