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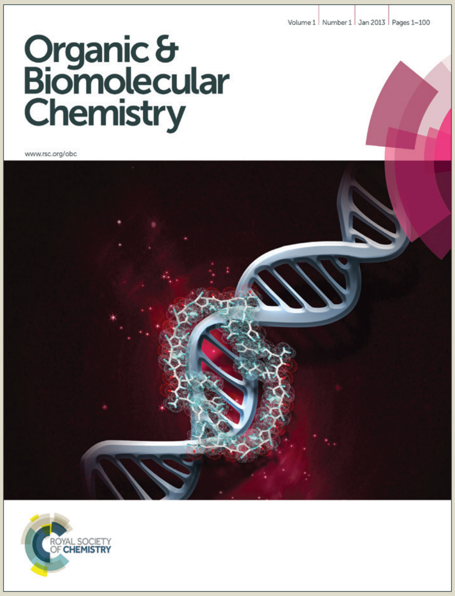

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ARTICLE TYPE

Gold(I)-Catalyzed Hydroindolylation of Allenyl Ethers†

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The gold (I)-catalyzed reaction/rearrangement of allenyl ethers has been investigated in the presence of indoles.Either hydroindolylation or alkylation of indole with the pendant group of allenyl ether has been observed. The reaction outcome seems to be decided mainly by the nature of the pendant group of the allenyl ether. Control experiments are indicative of an inner sphere mechanism for the hydroindolylation reaction.

Allenes are simple three carbon synthetic building blocks having three consecutive carbons which can be differentially functionalized with equal ease.[1] Arguably, gold catalysts, because of their soft and carbophilic character, have been well explored in recent times for the intermolecular and, more particularly, the intramolecular functionalization of allenes.[2–9] The gold-catalyzed hydroalkoxylationand hydroaminationof allenes has been well explored by the groups Yamamoto, Hashmi and Widenhoefer.[5-8] Comparatively, the gold-catalyzed hydroarylation of allenes is less explored.[4,9] The gold-catalyzed conjugate addition of the furans to the electron deficient allenes by Hashmi and co-workers,[4a] the intermolecular hydroarylation of allenes employing di- and trimethoxybenzene derivatives as nucleophiles by Gagne and co-workers,[4c] the intra- and intermolecular hydroindolylation of (electronically unbiased) allenes by Widenhoefer and co-workers[4b,9c] are the only few notable reports documented so far in this area. Keeping in mind the fact that there are very limited examples of the arylation with the allenes and that the functionalized indoles are valuable synthons in the area of total synthesis, we intended to explore the possibility of the hydroindolylation of allenyl ethers under the gold-catalysis.

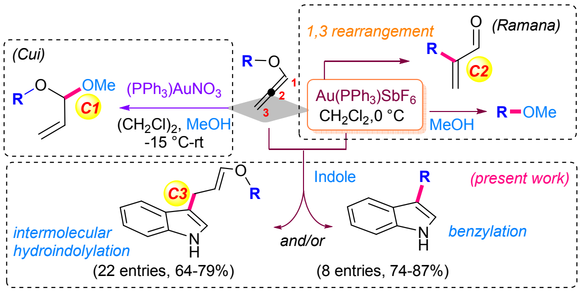
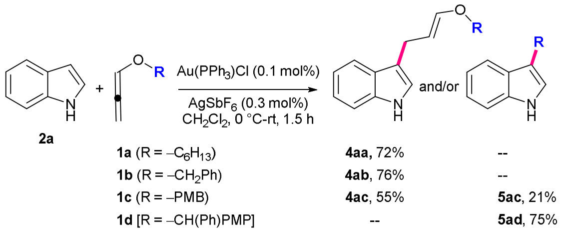


Figure 1: *Gold-catalyzed functionalization of allenyl ethers*

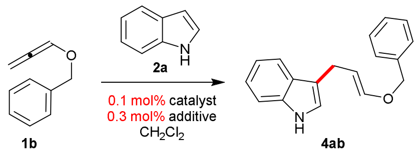
We speculated three possible products from the gold(I)-catalyzed reaction of allenyl ethers when there is an external C-nucleophile such as indole is present in the reaction medium. The addition can occur either at C1, like it was observed with the oxygen nucleophiles[10] or at C3, which is desired. On the other hand, if the fast [1,3] O→C rearrangement of these allenyl ethers is the first event, it will result in the isolation of the corresponding acryl aldehyde (Figure 1).[11]

To start in this direction, the four allenyl ethers **1a–1d** have been selected as the model allene substrates, considering their increasing ease of stabilization of the intermediate benzyl cation, thereby increasing the possibility of the [1,3]O→Crearrangement. The reactions were conducted by adding a freshly prepared CH_2Cl_2 solution of $AuCl(PPh_3)$ and $AgSbF_6$ (0.1 mol% Au with respect to the indole **2a**) to a cooled solution of indole and allene in $CH_2Cl_2$and left over for 1.5 h at rt. The results are surprising and complementary in nature with the allenyl ethers**1a**/**1b** and **1d**. As shown in Scheme 1 with the allenes **1a** and **1b**, the products **4aa** and **4ab** resulting from the hydroindolylation have been isolated. With**1d**,the C3benzylation was the only event giving**5ad**as the main product. The possibility of the C1 activation was eliminated with the C3 benzylation of indole.



Scheme 1: *The complementary reactivity of the allenyl ethers* **1a–1d**

Table 1:*Catalyst screening for hydroindolylation of allenyl ethers*



Entry	*Catalyst*	*Additive*	*Yield*
1	$AuCl(PPh_3)$	--	no reaction
2	$AuCl(PPh_3)$	$AgSbF_6$	72%
3	--	$AgSbF_6$	15%
4	--	AgOAc	no reaction
5	--	$AgNTf_2$	no reaction
6	--	$AgBF_4$	no reaction
7	$AuCl(PPh_3)$	$AgNTf_2$	no reaction
8	$AuCl_3$ or $AuBr_3$	--	~32%

On the other hand, in case of the reaction of **1c** with indole **2a**, mixture of **4ac** and **5ac** were observed. Quite interestingly, no formation of the [1,3] O→C rearrangement product was noticed with any of the four allenyl ethers used. This is very important since the allenyl ethers **1c** and **1d** undergo instantaneous rearrangement even with 0.05 mol% of the same catalyst in the absence of indole.[11]

Next, the compatibility of other Au-catalytic systems for the hydroindolylation reaction has been examined by keeping the indole **2a** and benzyl allenylether **1b** as the representative substrate. As shown in Table 1, the Au(I) complex alone has no influence on the reaction (entry 1). With $AgSbF_6$alone,only trace amounts of product was formed and the remaining allenyl ether decomposed. With other additives like AgOAc, $AgNTf_2$ and $AgBF_4$salts, no product formation was observed individually or in combination with $AuCl(PPh_3)$. Interestingly,in the case of allenamides, the nucleophilic addition was smooth with the $AgNTf_2$ in combination with gold(I) complex.[12] With both $AuCl_3$ and $AuBr_3$ salts, the hydroindolylation reaction was the major event. However, this resulted only in 32% of the product **4ab**.

The generality of these complementary reactions (Table 2) has been explored by employing two sets of allenyl ethers that mainly differ on the ease of the benzylic carbocationformations. All the reactions were carried out by employing 0.1 mol% of the catalyst solution. Initially, various *p*-(floro/chloro/bromo)-benzylallenylethers**1e**–**1g** were screened for the hydroindolylationpurpose and delivered the corresponding products **4ae**–**4ag** in 71–73% yield. Not only the simple benzylallenyl ethers but also the allenyl ethers bearing a fused ringlike2-napthylmethyl, 1-napthylmethylallenyl ethers **1i** and **1j** are also found to be good substrates for this hydroindolylation process. The reactions of the tetrahydrofurfurylmethylallenylether **1k** and 2,6-diflorobenzylallenylether **1h** were also found to be successful for the hydroindolylation with indole.

Also employed were various substituted indoles to study the influence of the nucleophilicity on the reaction outcome. The reactions with the 1-Me- (**2b**) 5-methoxy- (**2c**) and 5-bromoindole (**2d**) and 2-methyl-5-methoxy- (**2e**) indoles with selected allenyl ethers proceeded smoothly with excellent yields. On the other hand, the reactions of indole **2a**with the electron rich allenyl ethers **1n**–**1s** exclusively provided the benzylation products **5an**–**5as** respectively.

Quite interestingly, the mechanistic studies on these gold-catalyzed allene functionalization[14] with the external nucleophiles are scarce. In general, two pathways comprising either an inner sphere or an outer sphere coordination of gold with indole[15] and/or allene have been postulated. While, an inner sphere pathway has been proposed for the gold(III)-catalyzed intermolecular hydroamination of allenes by Yamamoto,[5a] for the same reaction, when gold(I) was employed, an outer sphere pathway was suggested by Toste.[5d] The possibility of both inner and outer sphere pathways has been speculated for intermolecular hydroamination and also for the addition of the furans to allenes respectively by the Widenhoefer and Hashmi groups.[5b, 4a] Coming to the hydroindolylation of allenes, an outer sphere pathway has been suggested by both the Widenhoefer and Che groups.[4b,4d] Thus, the issue of inner *vs* outer sphere pathways in the gold-catalyzed nucleophilic addition to allenes still remains an open question.

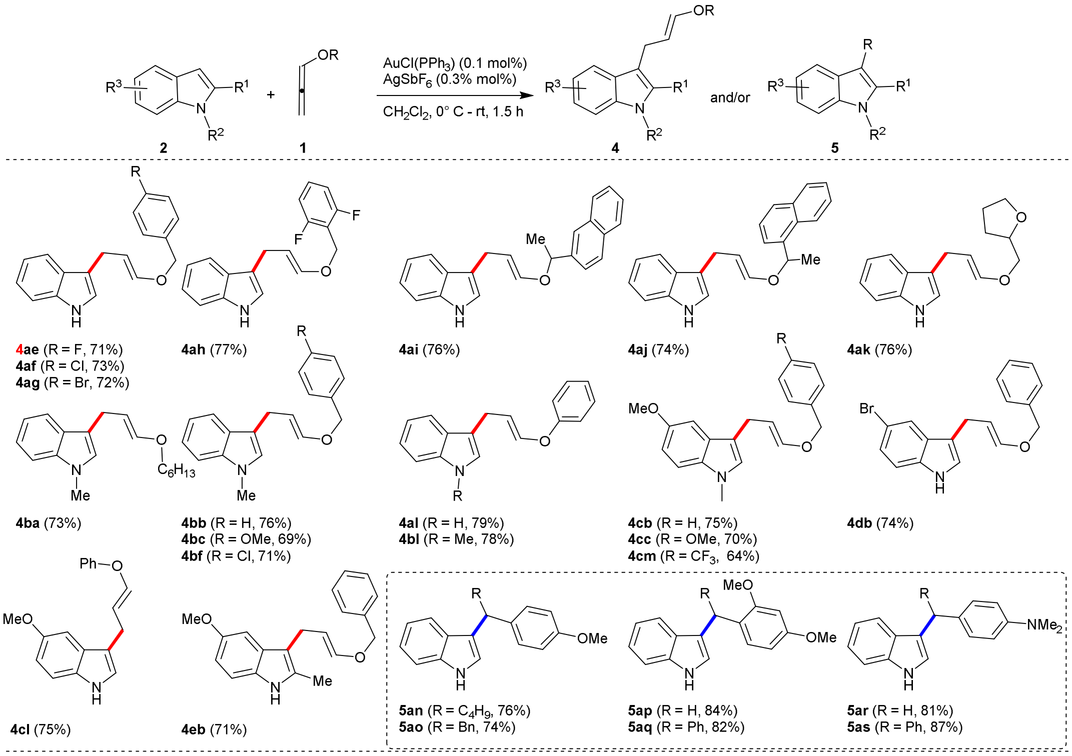
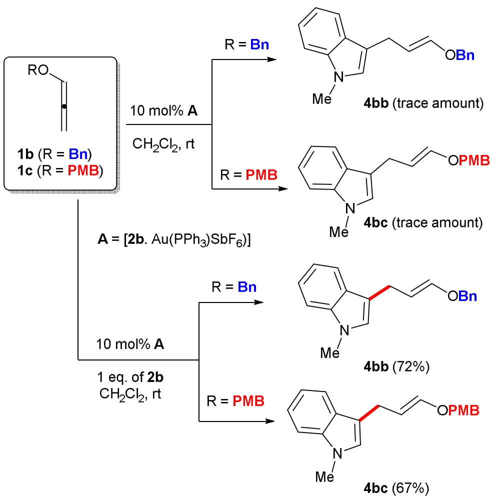


Table 2: *Scope of complementary alkylation or benzylation of indoles with allenyl ethers*

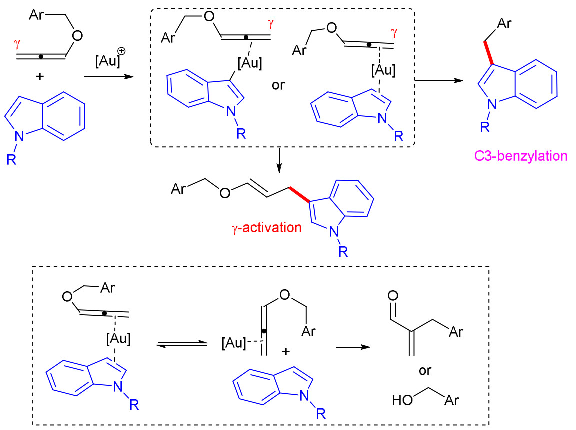
Given the observed dependence of the reaction outcome on electronic effects associated with the the allene, we conducted some control experiments with the pre-mixed indole gold solution [**2b**. Au(PPh$_3$)SbF$_6$)] as catalystto examine the feasibility of both [1,3] rearrangement [without any indole in the reaction mixture] and the hydroindolylation [with indole] of allenyl ethers **1b** and **1c**.As shown in Scheme 2, with this pre-complex [**2b.** Au(PPh$_3$)SbF$_6$)], only a trace amount of hydroindolylation products **4bb** and **4bc** was observed with the allenyl ethers **1b** and **1c.** On the other hand, in the presence of 1 eq. N-methylindole(**2b**), both allenyl ethers **1b** and **1c** gave the good yields of the corresponding hydroindolylation products.



Scheme 2:*The reactivity of allenyl ethers* **1b** *and* **1c** *with pre-complex***A***in the absence and in the presence of indole* **2b**

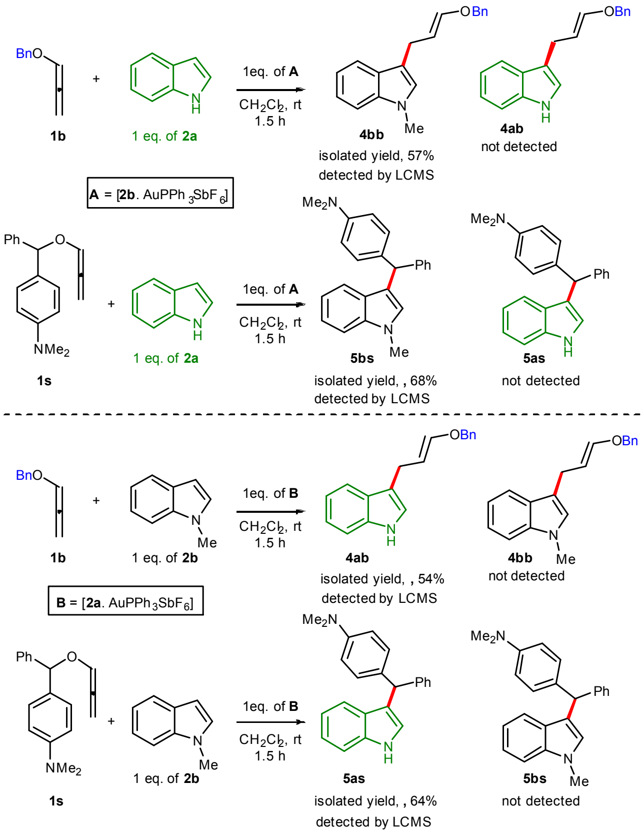
From the above control experiments, it is very clear that the complexation of **2b**with the gold-center is the first event and the subsequent transfer of the N-methylindole from the metal complex to the allenyl ethers **1b** and **1c** was evidenced by the formation of trace amounts of the hydroindolylation products **4ab** and **4bc**.[16]Notably, the resulting complex is not sufficiently active to bring the rapid [1,3]-rearrangement of the allenyl ether **1c**.[11]The Plausible mechanism was depicted in the Figure 2.

Figure 2:*Proposed mechnistic pathway for the gold(I) catalyzed hydroindolylation/benzylation of allenyl ethers*



These observations strongly suggest that an inner sphere coordination path is in operation for the corresponding hydroindolylation reactions (Figure 2). The pattern of ^{1}H NMR of *N*-methylindole has been completely changed when recorded in the presence of 1 eq. of Au(PPh$_3$)SbF$_6$ indicating possible interaction of gold-complex with indole. However, the ^{31}P spectra did not provided any conclusive information (See ESI). Hence, to further understand the involvement of an inner sphere mechanism in these two complementary hydroindolylation/benzylation reactions, an equimolar mixture of the allenyl ether **1b** and indole **2a** has been treated with 1eq. of catalyst solution **A** (prepared from the *N*-methylindole **2b**. The LC-MS analysis of the reaction indicated the formation of **4bb** resulting from the hydroindolylation with the *N*-methylindole **2b** that was present with the gold-complex (for complete experimental details see ESI). The product expected from hydroindolylation with externally present indole **2a** was not detected. Next, the benzylation reaction was examined with an equimolar mixture of allenyl ether **1s**, and indole **2a** has been treated with 1eq. of catalyst solution **A**. Once again, the LCMS analysis clearly indicated the exclusive benzylation of the *N*-methylindole **2b** present on the gold-complex (Scheme 3). Similarly, when added 1 eq. of complex **B** [indole **2a**/AuPPh$_3$SbF$_6$] to an equimolar solution of *N*-methylindole and allenes **1b** or **1s**, in both the instances, the exclusive transfer of indole **2a** only was observed.

Scheme 3: *Competition experiments in support of the inner sphere mechanism*



These stoichiometric experiments clearly indicated that the indole transfer either to the allene or to the carbocation of the contact ion pair (resulting from the dissociation of the allenyl ether) is occurring intramolecularly *inter alia* an outer sphere mechanism can be ruled out and probably the reaction path proceeds via an innersphere mechanism.

In conclusion, the gold (I)-catalyzed hydroindolylation of allenylethers has been investigated. Preliminary control experiments reveal that the key C–C bond formation event, i.e the nucleophilic addition to allene seems to be proceeding *via* an inner sphere pathway. However, further studies are warranted to provide conclusive evidence in this regard and also to understand the nature of the intermediates/transition states involved in this process.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Characterization data and spectra of all new compounds]. See DOI: 10.1039/b000000x/

1 a) D. R. Taylor, *Chem. Rev.,*1967, **67**, 317; b) S. M. Ma, *Pure Appl. Chem.,*2006, **78**, 197; c) M. Brasholz, H.-U. Reissig and R. Zimmer, *Acc. Chem. Res.,*2009, **42**, 45; d) E. Soriano and I. Fernández, *Chem. Soc. Rev.,*2014, **43**, 3041; e) E. Kraka and D. Cremer, *WIREs ComputMolSci.,* 2014, **4**, 285.

2 Selected reviews on allene activation by gold: a) A. Hoffmann-Röder and N. Krause, *Org. Biomol. Chem.,* 2005, **3**, 387; b) A. S. K. Hashmi and G. Hutchings, *Angew. Chem. Int. Ed.,* 2006, **45**, 7896; c) A. S. K. Hashmi, *Chem. Rev.,* 2007, **107**, 3180; d) A. Arcadi, *Chem. Rev.,* 2008, **108**, 3266; e) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.,* 2008, **108**, 3326; f) A. S. K. Hashmi and M. Rudolph, *Chem. Soc. Rev.,* 2008, **37**, 1766; g) N. D. Shapiro and F. D. Toste, *Synlett* 2010, 675; h) A. Corma and A. Leyva-Pérez M. J. Sabater, *Chem. Rev.,* 2011, **111**, 1657; i) M. Rudolph and A. S. K. Hashmi, *Chem. Commun.,* 2011, **47**, 12889; j) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358; k) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, *Chem. Rev.*, 2011, **111**, 1954; l) N. T. Patil, R. D. Kavthe and V. S. Shinde, *Tetrahedron*, 2012, **68**, 8079; m) N. T. Patil, *Chem. Asian J.*, 2012, **7**, 2186.

3 Selected reviews: a)D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.,*2008, **108**, 3351; b) N. Krause and C. Winter, *Chem. Rev.,*2011,**111**, 1994; c) C. Obradors and A. M. Echavarren, *Chem. Commun.,*2014, **50**, 16.

4 Selected papers on intermolecular hydroarylation: a) A. S. K. Hashmi, L. Schwarz, J. H. Choi and T. M. Frost, *Angew. Chem. Int. Ed.,* 2000, **39**, 2285; b) K. L. Toups, G. T. Liu and R. A. Widenhoefer, *J. Organomet. Chem.,* 2009, **694**, 571; c) M. A. Tarselli, A. Liu and M. R. Gagné, *Tetrahedron* 2009, **65**, 1785; d) M.-Z. Wang, C.-Y. Zhou, Z. Guo, E. L.-M. Wong, M.-K. Wong and C.-M. Che, *Chem. Asian J.,* 2011, **6**, 812; e) R. K. Kawade, P.-H. Huang, S. N. Karad and R.-S. Liu, *Org. Biomol. Chem.,* 2014, **12**, 737.

5 Selected papers on intermolecular hydroamination: a) N. Nishina and Y. Yamamoto, *Angew. Chem. Int. Ed.,* 2006, **45**, 3314; b) R. E. Kinder, Z. Zhang and R. A. Widenhoefer, *Org. Lett.,*2008, **10**, 3157; c) X. Zeng, M. Soleilhavoup and G. Bertrand, *Org. Lett.,* 2009, **11**, 3166; d) Z. J. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, III and F. D. Toste, *J. Am. Chem. Soc.,* 2010, **132**, 13064; e) K. L. Butler, M. Tragni and R. A. Widenhoefer, *Angew. Chem. Int. Ed.,* 2012, **51**, 5175; f) C. Hurtado-Rodrigo, S. Hoehne and M. P. Muñoz, *Chem. Commun.,* 2014, **50**, 1494.

6 Selected papers on intermolecular hydroalkoxylation: a) N. Nishina and Y. Yamamoto, *Tetrahedron Lett.,* 2008, **49**, 4908; b) Z. Zhang and R. A. Widenhoefer, *Org. Lett.,* 2008, **10**, 2079; c) Z. Zhang, S. Du Lee, A. S. Fisher and R. A. Widenhoefer, *Tetrahedron* 2009, **65**, 1794; d) G. Wang, Y. Zou, Z. Li, Q. Wang and A. Goeke, *Adv. Synth. Catal.,* 2011, **353**, 550.

7 Selected papers on intramolecular hydroamination: a) N. Morita and N. Krause, *Org. Lett.,* 2004, **6**, 4121; b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian and R. A. Widenhoefer, *J. Am. Chem. Soc.,* 2006, **128**, 9066; c) Z. Zhang, C. F. Bender and R. A. Widenhoefer, *J. Am. Chem. Soc.,* 2007, **129**, 14148; d) R. L. LaLonde, B. D. Sherry, E. J. Kang, and F. D. Toste, *J. Am. Chem. Soc.,* 2007, **129**, 2452; e) C. Winter and N. Krause, *Angew. Chem. Int. Ed.,* 2009, **48**, 6339; f) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner and F. D. Toste, *Angew.Chem. Int. Ed.,* 2010, **49**, 598.

8 Selected papers on intramolecular hydroalkoxylation: a) A. S. K. Hashmi, M. C. Blanco, D. Fischer and J. W. Bats, *Eur. J. Org. Chem.,* 2006, 1387; b) C. Y. Zhou, P. W. H. Chan and C. M. Che, *Org. Lett.,* 2006, **8**, 325; c) C. J. T. Hyland and L. S. Hegedus, *J. Org. Chem.,* 2006, **71**, 8658; d) B. Gockel and N. Krause, *Org. Lett.,* 2006, **8**, 4485; e) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science* 2007, **317**, 496; f) Z. Zhang and R. A. Widenhoefer, *Angew. Chem. Int. Ed.,* 2007, **46**, 283; g) Y. Shi, K. E. Roth, S. D. Ramgren and S. A. Blum, *J. Am. Chem. Soc.,* 2009, **131**, 18022; h) B. Gockel and N. Krause, *Eur. J. Org. Chem.,* 2010, 311.

9 Selected Papers on intramolecular hydroarylation: a) N. Marion, S. Díez-González, P. de Frémont, A. R. Noble and S. P. Nolan, *Angew. Chem. Int. Ed.,* 2006, **45**, 3647; b) Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.,* 2006, **128**, 10352; c) C. Liu and R. A. Widenhoefer, *Org. Lett.,* 2007, **9**, 1935; d) X. Huang and L. Zhang, *J. Am. Chem. Soc.,* 2007, **129**, 6398; e) J. H. Lee and F. D. Toste, *Angew. Chem. Int. Ed.,* 2007, **46**, 912; f) T. Watanabe, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.,* 2007, **9**, 4821; g) D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem. Int. Ed.,* 2009, **48**, 5733; h) J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino and J. M. González, *Chem. Eur. J.,* 2010, **16**, 11827; i) R. M. Zeldin and F. D. Toste, *Chem. Sci.,* 2011, **2**, 1706; j) B. Chen, W. Fan, G. Chai and S. Ma, *Org. Lett.,* 2012, **14**, 3616.

10 D-M. Cui, Z-L.Zheng and C. Zhang, *J. Org. Chem.,* 2009, **74**, 1426.

11 C. N. Kona and C. V. Ramana, *Chem. Commun.,* 2014, **50**, 2152.

12 a) M. C. Kimber, *Org. Lett.,* 2010, **12**, 1128; b) G.-H.Li, W. Zhou, X.-X. Li, Q.-W. Bi, Z. Wang, Z.-G. Zhao, W.-X. Hu and Z. Chen, *Chem. Commun.,* 2013, **49**, 4770.

13 For Au(I)-catalyzed C3-benzylation of indoles: H. Hikawa, H. Suzuki and I. Azumaya, *J. Org. Chem.,* 2013, **78**, 12128

14 Selected papers and reviews on mechanism: a) E. Mizushima, T. Hayashi and M. Tanaka, *Org. Lett.,* 2003, **5**, 3349; b) R. A. Widenhoefer and X. Han, *Eur. J. Org. Chem.,* 2006, 4555; c) R. S. Paton and F. Maseras, *Org. Lett.,* 2009, **11**, 2237; d) L.-P. Liu and G. B. Hammond, *Chem. Asian J.,* 2009, **4**, 1230; and 5c; e) N. Nishina and Y. Yamamoto, *Tetrahedron* 2009, **65**, 1799; f) M. Malacria, L. Fensterbank and V. Gandon, *Top CurrChem.,* 2011, **302**, 157; g) J. H. Kim, S.-W. Park, S. R. Park, S. Lee and E. J. Kang, *Chem. Asian J.,* 2011, **6**, 1982; h) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.,* 2011, **40**, 1910; i) W. Yang and A. S. K. Hashmi, *Chem. Soc. Rev.,* 2014, **43**, 2941.

15 Some papers on aurated indole intermediates: a) A. Arcadi, G. Bianchi, M. Chiarini, G. D'Anniballe and F. Marinelli, *Synlett* 2004, 944; b) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi and F. Marinelli, *J. Org. Chem.,* 2005, **70**, 2265; c) V. Pirovano, M. Dell'Acqua, D. Facoetti, D. Nava, S. Rizzato, G. Abbiati and E. Rossi, *Eur. J. Org. Chem.,* 2013, 6267.

16 We sincerely thak one of the reviewers for suggesting $[Au(PPh_3)_2]^+$ as a possible alternative for the LC-MS peak at 721.10 m/z noticed for complex **A** which, accidentally, also matches with the bis indolyl.AuPPh$_3$ (See ESI). A HRMS analysis clearly suggested it as $[Au(PPh_3)_2]^{+.}$

17 M. Kumar, J. Jasinski, G. B. Hammond and B. Xu, *Chem. Eur. J.,* 2014, **20**, 3113.

Graphical Abstract:

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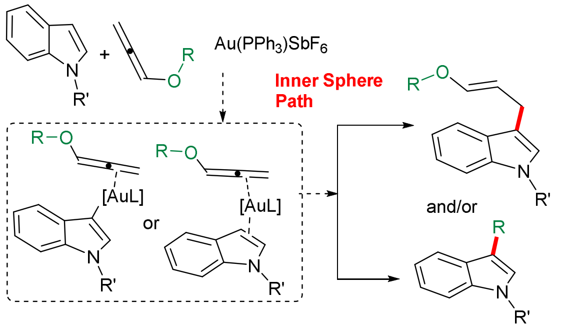
Chandrababu Naidu Kona, Mahesh H. Sinde and Chepuri V. Ramana



Nucleophilicity Game: The gold (I)-catalyzed reactions/rearrangement of allenyl ethers has been investigated in the presence of indoles. Either hydroindolylation or alkylation of indole with the pendant group of allenyl ether has been noticed. The reaction outcome seems to be decided mainly by the nature of pendant group of allenyl ether. Control experiments are indicative of an inner sphere mechanism for the hydroindolylation reaction.