

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/275045982>

ChemInform Abstract: Sequential Friedel–Crafts–Type α -Amidoalkylation/Intramolecular Hydroarylation: Distinct Advantage of Combined Tf₂NH/Cationic LAu(I) as a Consecutive or Bina...

ARTICLE *in* ORGANIC LETTERS · APRIL 2015

Impact Factor: 6.36 · DOI: 10.1021/acs.orglett.5b00718 · Source: PubMed

CITATION

1

READS

42

8 AUTHORS, INCLUDING:



Liliana Boiaryna

Université d'Orléans

2 PUBLICATIONS 15 CITATIONS

SEE PROFILE



Mohamed Othman

Université du Havre

45 PUBLICATIONS 339 CITATIONS

SEE PROFILE



Malika trabelsi ayadi

University of Carthage laboratoire LACRESNE ...

151 PUBLICATIONS 859 CITATIONS

SEE PROFILE



Vincent Dalla

Université du Havre

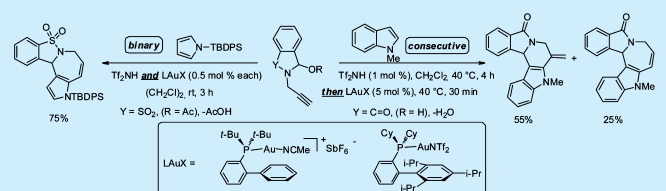
41 PUBLICATIONS 617 CITATIONS

SEE PROFILE

Sequential Friedel–Crafts-Type α -Amidoalkylation/Intramolecular Hydroarylation: Distinct Advantage of Combined Ti_2NH /Cationic $\text{LAu}(\text{I})$ as a Consecutive or Binary Bicataltic SystemLiliana Boiaryna,^{§,†} Mohamed Salah Azizi,^{§,†,‡} Abderrahman El Bouakher,[†] Baptiste Picard,[†] Catherine Taillier,[†] Mohamed Othman,[†] Malika Trabelsi-Ayadi,[‡] and Vincent Dalla^{*,†}[†]Unité de Recherche en Chimie Organique et Macromoléculaire (URCOM, EA 3221, FR CNRS 3038), Faculté des Sciences et Techniques, l'Université du Havre, 25 rue Philippe Lebon, BP 540, Le Havre 76058 Cedex, France[‡]Laboratoire d'Application de la Chimie aux Ressources et Substances Naturelles et à l'Environnement-LACReSNE-Faculté des Sciences de Bizerte, Université de Carthage, 7021 Bizerte, Tunisie

S Supporting Information

ABSTRACT: The combined use of Ti_2NH and $\text{L}(\text{Au})^+\text{X}^-$ as a dual or binary catalytic system clearly improves the efficiency and enlarges the scope of the tandem intermolecular Friedel–Crafts α -amidoalkylation/intramolecular hydroarylation sequence, compared to an “all gold” multicatalysis approach.



Taken separately, *N*-acyliminium ion chemistry¹ and gold catalysis² are foundational to modern organic synthesis. Given their immense individual potential, these two fundamental research areas hold the potential to be merged to provide interesting new avenues in organic synthesis. In particular, the dual hard/soft character exhibited by gold complexes along with the high construction flexibility of *N*-acyliminium ion precursors, with notably easy installation of alkynes or allene functions, offer a vast array of possible combinations which can provide multiple synthetic opportunities. This unlimited potential still remains largely untapped, and seminal studies have only recently emerged from a few research groups. So far, two general approaches have been considered for the combination of these two topics, including a step-by-step approach wherein the *N*-acyliminium step and the gold-catalyzed event are engineered in a distinct manner³ and a cascade and/or tandem sequence wherein the manipulation of a transient *N*-acyliminium salt and the gold-catalyzed step(s) are occurring in the same reaction vessel.⁴ We have recently contributed to this endeavor by devising an intermolecular Friedel–Crafts amidoalkylation/intramolecular hydroarylation sequence using $\text{AuNTf}_2/\text{Ph}_3\text{PAuNTf}_2$ as a model couple of hard and soft gold catalysts.⁵ We now report a significant improvement of this chemistry by presenting new results demonstrating that the limitations displayed by the “all gold” approach are only partially solved by tuning the hydroarylation gold catalyst LAuX but in contrast are broadly overcome by exchanging a Brønsted super acid for AuNTf_2 . This mechanism-designed new application of combined Brønsted acid and gold catalysis,⁶ although at first glance looks like a small variation, in practice significantly improves the chemical efficiency and expands the scope of this tandem sequence by providing a wide variety of relatively sophisticated polyanellated structures from trivial *N,O*-acetals with general good efficiency.

In our previous report, acceptable yields of the desired compounds were isolated on subjecting mixtures of *N,O*-acetal **1** and aromatic nucleophiles to the consecutive addition of AuNTf_2 and the Gagosz catalyst **CAT.1** (Figure 1) as depicted in Scheme

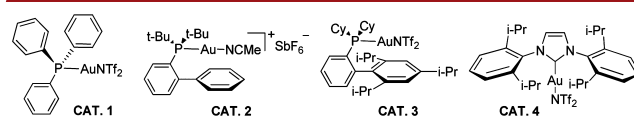
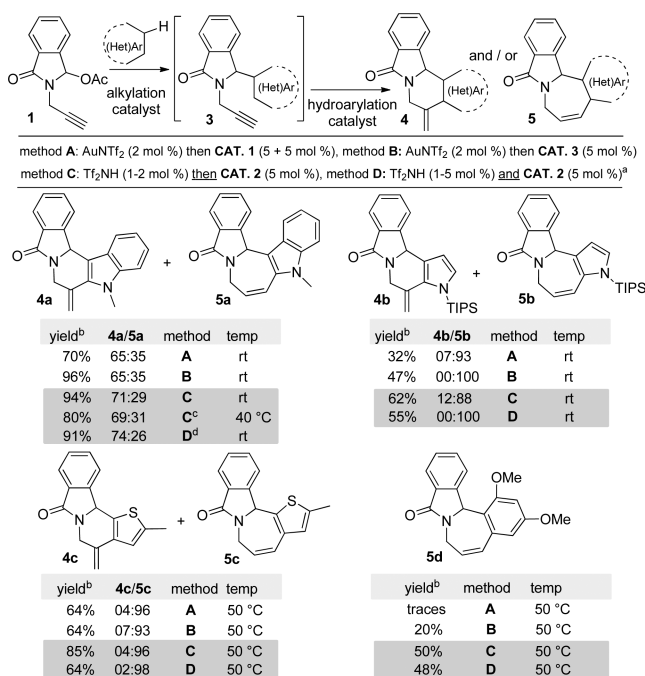


Figure 1. Selection of carbophilic gold catalysts.

1 (method A).⁵ However, our optimized procedure was far from ideal, requiring a high catalyst loading of 10 mol % in a somewhat tedious portionwise addition mode. Moreover, only in the reaction of *N*-methylindole were acceptable yields of the hydroarylation products (obtained as a separable mixture of the 6-*exo* product **4a** and the rather unexpected 7-*endo* isomer **5a**)⁷ obtained. The other aromatics indeed gave at best only moderate yields of the expected products **4b–c/5b–d**, which were much lower than those of the hydroarylation carried out on the isolated Friedel–Crafts adducts **3** (see Scheme 1 for the generic structure of these FC products).⁸ As most relevant limitations, the reaction of 1,3-dimethoxybenzene gave only trace amounts of **5d**, most likely as a result of a slow hydroarylation even at 80 °C.^{8,9} Another stringent problem is the poor global yield (32–2% of **4b** + 30% of **5b**) recorded for the reaction of *N*-TIPS-pyrrole, despite observation of full conversion. However, and remarkably, a uniform, quite unusual, and unpredicted high 7-

Received: March 11, 2015

Published: April 15, 2015

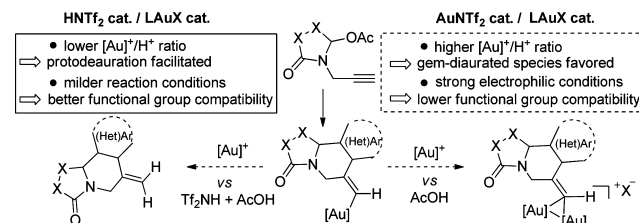
Scheme 1. Tandem F–C α -Amidoalkylation/Hydroarylation of Acetoxy Lactam **1a: Optimization Study**

^aUnless otherwise indicated, all reactions were performed on the acetoxy lactam **1**, and the details on the experimental conditions are given in the Supporting Information. ^bThe combined yields of the 6-exo and 7-endo products are given for nonselective reactions, and the ratios given are determined from the isolated yields of each regioisomer; isolated yields of the endo hydroarylation products are given. ^cThe reaction was carried out from the accordant hydroxy lactam **6**. ^dWith CAT.4, only the 6-exo product **4a** was isolated, but in only 67% yield.

endo selectivity (see preferential formation of **5b–d**) was observed.⁷

Following these encouraging but still improvable results, we elected to use the more robust Echavarren type catalysts CAT.2–4^{2,7a,c–f,i} (Figure 1), and the new results thereof are depicted in Scheme 1, method B). Even if only 5 mol % of CAT.2/3 was sufficient to achieve full conversion for any combinations explored, only *N*-methylindole did really benefit from this new procedure, with isolation of **4a** + **5a** in a nearly quantitative yield. Limitations still remained for the other aromatics, which all gave the desired products in slightly improved yields that were still unsatisfactory. Worthy of note, switching from CAT.1 to CAT.2/3 allowed the regioselectivity profile of these cascade reactions to remain unchanged, thereby suggesting that the substrate/nucleophile combination dominates the influence of the catalyst in the control of these tandem reactions. From this set of results we suspected the rate acceleration observed in most of the tandem processes compared to their parent hydroarylation⁸ step might be due to the release of 1 equiv of acetic acid in the medium, which should facilitate protodeauration of the vinylgold intermediate at the expense of any potentially competing generation of *gem*-diaurated intermediates.¹⁰ We therefore speculated that the orchestration of an even faster protodeauration step would implicitly limit the well-recognized adverse effects potentially caused when a concurrent *gem*-diauration event occurs to an excessive extent, which is more likely to occur when both alkylation and cyclization steps are gold-catalyzed¹⁰ as is the case with our procedures A and B. We,

therefore, assumed that replacing AuNTf₂ by Tf₂NH would offer a very simple solution to this issue¹¹ while still maintaining high efficiency of the intermolecular FC alkylation,¹² which is also critical for the success of our cascade manifold (Scheme 2). By

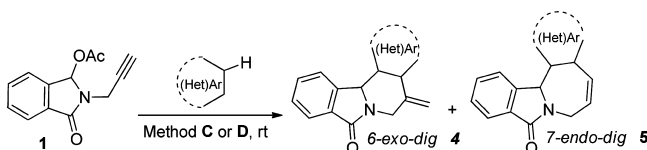
Scheme 2. Working Hypothesis for a More Efficient Second-Generation Tf₂NH/LAuX Combination

creating in this way a milder reaction medium, we were also expecting to improve the functional group compatibility as, for example, a limitation of the desilylation problem we suspected to occur extensively in the reaction of **2b** (Scheme 1) as a result of too aggressive conditions associated with the use of AuNTf₂ (Scheme 2).

Reaction feasibility was verified on the tandem reaction of *N*-methylindole. As anticipated, we observed that application of the consecutive addition of Tf₂NH and CAT.2–3 to a mixture of **1** and **2a** gave similar performances as the AuNTf₂/CAT.3 system (Scheme 1, method C). Gratifyingly, method C also tolerates the use of hydroxy lactam **6**, thereby establishing an improved step and atom-economy protocol that releases 1 equiv of water as the only byproduct (see footnote c in Scheme 1). The potential of this new dual combination of catalysts was extended further by orchestration of a truly binary approach with a simultaneous inclusion of the two catalysts in the reaction vessel, affording **4a** + **5a** in an excellent global yield of 91% (method D in Scheme 1).¹³ With two robust procedures C and D in hand for this cascade bicatalytic alkylation/hydroarylation sequence, we next sought to further establish the reaction scope. We initiated this effort by reinvestigating *N*-TIPS-pyrrole **2b**, 2-methylthiophene **2c**, and 1,3-dimethoxybenzene **2d** as binucleophiles (Scheme 1, results shown in frames). Commensurate with our assumption, their tandem reactions took place with greater efficiencies than those performed with the two gold catalysts. Noticeably, **2c**¹⁴ gave on application of method C the 7-endo product **5c** in an excellent yield of 85% (versus 64% using the all-gold method, methods A and B), while the yield of **5d** measured from the reaction of **2d** grew by a significant level of 30%, now reaching a decent value of 50%. In agreement with the effect observed in the reaction of *N*-Me-indole, both procedures C and D performed about equally well in the reaction of the more sensitive *N*-TIPS-pyrrole **2b**, now consistently affording the desired pyrrolo-fused polyheterocyclic compounds **4b/5b** in around 55–65% yield with high 7-endo selectivity. We suspected a partial desilylation throughout the tandem sequence was again responsible for the moderate combined yield, and we were expecting to overcome this limitation by replacing *N*-TIPS-pyrrole with its more robust and unusual TBDPS analogue **2e**.^{15,16} While we observed that this binucleophile surpasses **2b** in several cases (vide infra), its reaction with **1** gave the desired product **5e** in a 55% yield comparable to that of **5b**, again with complete and unusual 7-endo selectivity (Table 1, entry 1).

Additional results that probe the scope of this new tandem transformation are also presented in Table 1 (entries 2–8). In general, both procedures C and D (using CAT.2) could be

Table 1. Reaction Scope of the Tandem F–C α -Amidoalkylation/Hydroarylation Sequence with TiF_2NH /L(Au(I)) as a Bicatalytic System



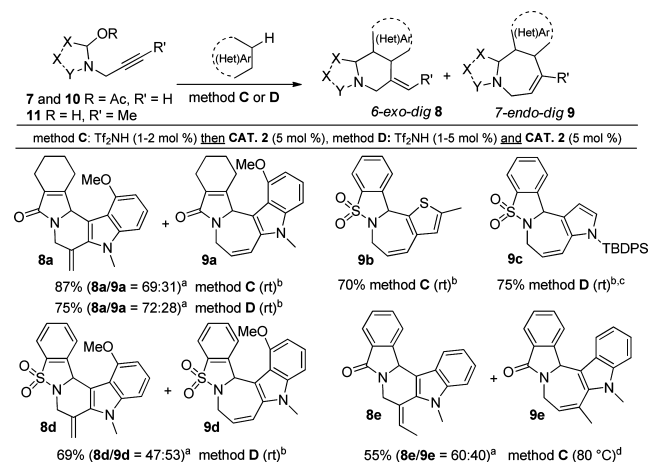
entry	Ar	products	method ^b	global yield	Ratio ^c 4/5
1	2e	4e/5e	D	55%	0:100
2	2f	4f/5f	C	88%	76:24
3	2g	4g/5g	D	97%	75:25
4	2h	4h/5h	C	90%	57:43
5	2i	4i/5i	D	52%	66:34
6	2j	4j/5j	C	77%	53:47
7	2k	4k/5k	C	77%	53:47
8	2l	4l/5l	D	71%	53:47

^aThe blue label indicates the site of the α -amidoalkylation, while the red label is for the site of hydroarylation. ^bMethod C: TiF_2NH (1 mol %) then CAT.2 (5 mol %). Method D: TiF_2NH (1–5 mol %) and CAT.2 (5 mol %). ^cDetermined from the isolated yields of each regioisomer.

applied with nearly equal success across a set of combinations of diverse *N*-alkylindoles **2** and *N,O*-acetal **1**. Compounds **2f–i** bearing substituents of diverse electronic properties at different positions were tolerated to give mixtures of the 6-*exo* and 7-*endo* products in good yields. The regiochemical profiles obtained throughout this exemplification study are in good agreement with the preliminary experiments furnishing **4a** + **5a**, showcasing systematic formation of mixtures of 6-*exo* and 7-*endo* products **4f–i** + **5f–i** in varying ratios that unfortunately do not exceed 70/30 (the initial **4a**/**5a** ratio).

Not only isoindolic substrates such as **1** and **6** (Scheme 1 and Table 1) but also their tetrahydro and saccharine analogues **7** and **10** were effective in producing, on reaction with **2f** (formation of **8a** + **9b** and **8d** + **9d**), 2-methylthiophene **2c** (formation of **9b**) and *N*-TBDPS-pyrrole **2e** (formation of **9c**), excellent results (Scheme 3) which are in perfect agreement with those outlined above. The saccharin substrate **10** was particularly responsive to the conditions of this cascade reaction, a feature that is nicely exemplified by the efficient and selective isolation of 720 mg of the 7-*endo* product **9c** (75% yield) from an experiment with TBDPS-pyrrole **2e** carried out on a 0.5 g scale at the remarkable catalyst loading of only 0.5 mol % for each TiF_2NH and CAT.2. In this case, use of *N*-TIPS-pyrrole **2b** produced substantially more side products and afforded the desired 7-*endo* product in only 50% yield (result not shown), thereby showcasing the value of TBDPS as a *meta*-directing and robust functional group in pyrrole chemistry.^{15,16} The high intrinsic reactivity of the saccharine backbone is also illustrated by the room-temperature hydroarylation with the thiophene derivative, while a similar sequence had to be executed at 50 °C in the phthalimide case.

Scheme 3. Reaction Scope of the Tandem F–C α -Amidoalkylation/Hydroarylation Sequence with TiF_2NH /L(Au(I)) as a Bicatalytic System



^aDetermined from the isolated yields of each regioisomers. ^bCarried out with the *N,O*-acetals **7** and **10** (OR = OAc). ^cPerformed on 500 mg of **10** with 0.5 mol % each of TiF_2NH and CAT.2. ^dCarried out on the hydroxy lactam **11** (OR = OH).

Finally, the catalytic tandem Friedel–Crafts/hydroarylation of the hydroxy lactam **11** bearing an internal alkyne with *N*-Me-indole **2a** also appeared to be feasible, affording the chromatographically separable products 6-*exo* **8e** and 7-*endo* **9e** in 55% global yield and a 60/40 ratio which is consistent with those recorded from the reactions of the terminal alkynes **1**, **6**, **7**, and **10**.^{8,17}

In summary, we have shown that the combined use of TiF_2NH and L(Au)⁺X[−] (with L = JohnPhos, X-Phos) as a consecutive or binary catalytic system improves the efficiency and enlarges the scope of the tandem intermolecular Friedel–Crafts α -amidoalkylation/intramolecular hydroarylation sequence of *N*-propargylic *N,O*-acetals, compared to a previously reported “all gold system”.⁵ Interestingly, the strongest effect of the Brønsted superacid versus the nonstabilized gold(I) catalyst is proposed not to facilitate alkylation but rather to positively influence the second hydroarylation step, a view that is expected to be a general trend beyond the specific sequence studied in this work. Unusual and rather counterintuitive 7-*endo* regioselectivities in the hydroarylation step of the sequence, as well as the synthetic usefulness of *N*-TBDPS-pyrrole as a robust nucleophile that retards desilylation and affords complete position selectivity in both steps of the sequence, constitute additional input provided by this study.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures, analytical data, and ¹H NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vincent.dalla@univ-lehavre.fr.

Author Contributions

§L.B. and M.S.A. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

L.B. thanks the "Region Haute-Normandie" and "the Réseau CRUNCH Orga" for a grant and financial support. M.S.A. is grateful to the Tunisian government for a scholarship and to AUF for financial support.

■ REFERENCES

- (1) Reviews: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339. (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513.
- (2) Reviews with a particular emphasis on the hydroarylation of alkynes: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Gorin, D. J.; Sherry, B. D.; Toste, D. F. *Chem. Rev.* **2008**, *108*, 3351. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Skouta, R.; Li, C. J. *Tetrahedron* **2008**, *64*, 4917. (f) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801. (g) Rudolf, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (h) Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575.
- (3) (a) Jury, J. C.; Swamy, N. K.; Yazici, A.; Willis, A. C.; Pyne, S. G. *J. Org. Chem.* **2009**, *74*, 5523. (b) Breman, A. C.; Dijkink, J.; van Maarseveen, J. H.; Kinderman, S. S.; Hiemstra, H. *J. Org. Chem.* **2009**, *74*, 6327.
- (4) (a) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. (b) Ji, X.; Zhou, Y.; Wang, J.; Zhao, L.; Jiang, H.; Liu, H. *J. Org. Chem.* **2013**, *78*, 4312. (c) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448. (d) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585. (e) Patil, N. T.; Shinde, V. K.; Sridhar, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221.
- (5) Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem.—Eur. J.* **2012**, *18*, 14192.
- (6) Reviews: (a) Hashmi, A. S. K.; Hubbert, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1010. (b) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 10212. Seminal contributions: (c) Reference 4a. (d) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (e) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4204.
- (7) As far as we are aware, all examples in the literature where cationic gold(I) complexes were applied in the hydroarylation of terminal alkynes follow an exclusive 6-*exo* selectivity: (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (b) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517. (c) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun.* **2011**, 218. (d) Pascual, S.; Bour, C.; de Mendoza, P.; Echavarren, A. M. *Beilstein J. Org. Chem.* **2011**, *7*, 1520. (e) Dong, Z.; Liu, C.-H.; Wang, Y.; Lin, M.; Yu, Z.-X. *Angew. Chem., Int. Ed.* **2013**, *52*, 14157. (f) Pan, B.; Lu, X.; Wang, C.; Hu, Y.; Wu, F.; Wan, B. *Org. Lett.* **2014**, *16*, 2244. The same trend is observed with AuCl₃ as catalyst: (g) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631. (h) A single report by Gagosz and colleagues describes hydroarylations where small amounts of 7-*endo* products were formed from terminal alkynes in addition to the usual 6-*exo* products: (i) Jurberg, I. D.; Gagosz, F. *J. Organomet. Chem.* **2011**, *696*, 37.
- (8) Every cascade reaction we have examined proceeded with identical regiocontrol as the accordant hydroarylation executed from the isolated F—C product **3**. Details on the results of these hydroarylations, as well as on the formation of side products formed in the cascade reactions, are given in the Supporting Information.
- (9) Although the overall nucleophilicity of 1,3-dimethoxybenzene is estimated to be greater than that of indole and 2-methylthiophene, the sluggish reactivity exhibited by **3d** could be attributed to the low local nucleophilicity of the carbon atom (with a red label in Table 1) to attack the alkyne—gold complex: Pratihari, S.; Roy, S. *J. Org. Chem.* **2010**, *75*, 4957.
- (10) For selected examples of papers focusing on *gem*-diaurated vinyl gold intermediates, see: (a) Weber, D.; Tarselli, M. A.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 5733. (b) Seidel, G.; Lehmann, C. W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8466. (c) Weber, D.; Jones, T. D.; Adduci, L. L.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2452. (d) Zhdanko, A.; Maier, M. E. *Chem.—Eur. J.* **2014**, *20*, 1918. (e) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wietek, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (f) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593.
- (11) For some gold-catalyzed hydroarylations which are facilitated by additional Tf₂NH, see: Shu, C.; Li, L.; Chen, C.-B.; Shen, H.-C.; Ye, L.-W. *Chem. Asian. J.* **2014**, *9*, 1525.
- (12) For our contribution in Tf₂NH-catalyzed Friedel—Crafts-type α -amidoalkylation reactions, see: (a) Devineau, A.; Pousse, G.; Taillier, C.; Rouden, J.; Blanchet, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, *352*, 2881. (b) Moussa, S.; Comesse, S.; Dalla, V.; Daich, A.; Netchitailo, P. *Synlett* **2011**, 2425.
- (13) A preliminary catalyst screening, notably using CAT.4, was undertaken and did not allow significant performance of the reaction; see footnote d in Scheme 1.
- (14) The successful use of thiophene derivatives in hydroarylation is quite rare. (a) See ref 7e for a single example with moderate yield. (b) For unsuccessful attempts, see: Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; van der Eycken, E. V. *Synthesis* **2013**, 2571.
- (15) Bulky *N*-silyl pyrroles were chosen for their ability to direct total *meta* selectivity in the Friedel—Crafts amidoalkylation, a feature not shared by pyrrole or *N*-Me-pyrrole. For a review discussing these properties of the commercially available *N*-TIPS-pyrrole, see: Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531.
- (16) Lancianesi, S.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2013**, *355*, 3285.
- (17) The gold-catalyzed hydroarylation of internal alkylalkynes is well documented, and its regioselectivity 6-*exo* versus 7-*endo* varies substantially as a function of the topology of the substrate. For examples with 6-*exo* selectivity, see: (a) Reference 7c. (b) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Sharma, S. K.; Parmar, V. S.; van der Eycken, E. V. *Chem. Commun.* **2012**, 10916. For examples with 7-*endo* selectivity, see: (c) Cera, G.; Crispino, P.; Monari, M.; Bandini, M. *Chem. Commun.* **2011**, 7803. (d) Reference 14b.