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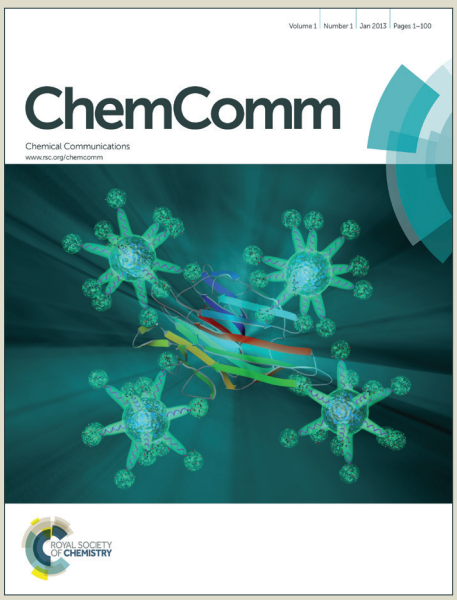

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Facile Synthesis of Fluorescent Active Triazapentalene through Gold-Catalyzed Triazole-Alkyne Cyclization

Cite this: DOI: 10.1039/x0xx00000x

Rong Cai,[a] Dawei Wang,[a] Yunfeng Chen,[a] Wuming Yan,[a] Natalie R. Geise,[a] Sripadh Sharma,[a] Huiyuan Li,[b] Jeffrey L. Petersen,[a] Minyong Li*[c] and Xiaodong Shi*[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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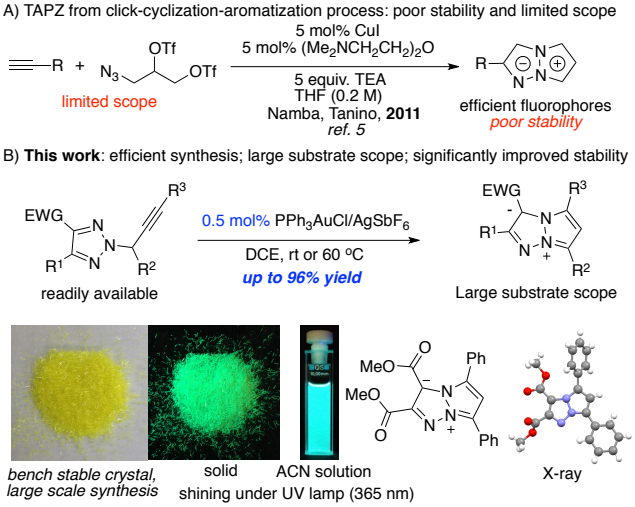
Fluorescent active triazapentalene zwitterions (TAPZ) were prepared through Au(I) catalyzed triazole-alkyne *5-endo-dig* cyclization. While effective gold catalyst turnover (0.5% loading, up to 96% yield) was achieved, the stability of these new 10-π-electron bicyclic structures was also significantly improved, which warranted future applications of these fluorescent dyes.

Pentalene is an extremely unstable compound (forming a dimer even at -100 °C) due to its *anti*-aromatic 8-π-electron structure.[1] With the addition of two more electrons to the conjugated system, the much more stable aromatic pentalenide anions have been reported in the past.[2] Similarly, azapentalenes adopt the 10-π-electron aromatic structures with overall neutral charge.[3] Although these compounds earned some attention as ligands in early 1980s,[4] their applications are limited due to the few available synthetic methods and narrow substrate scope.

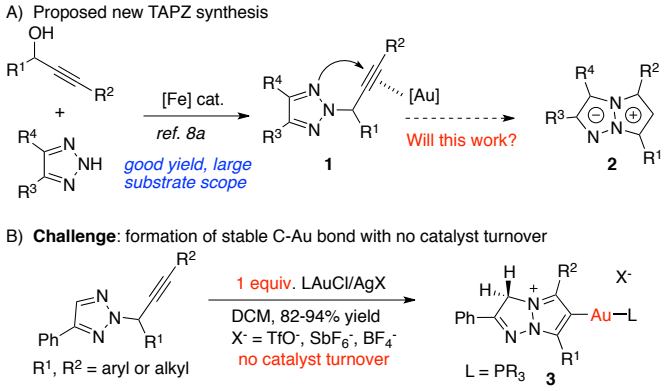
Recently, Namba and Tanino reported the synthesis of triazapentalene zwitterions (TAPZ, **Scheme 1A**) via cascade click-cyclization-aromatization.[5] One interesting observation was the good fluorescence emission of these TAPZ compounds in visible light region with λ_{max} between 380 nm to 560 nm. However, the "simple" triazapentalenes prepared from this method gave modest to poor stability especially under acidic conditions, which made them less practical fluorescent dyes for actual applications. Meanwhile, the reported synthetic route was only suitable for terminal alkynes (necessary for click chemistry) with highly reactive di-triflates, which significantly limited the substrate scope and prevented further development of these new fluorophores. Based on our recent studies in triazole-gold catalyzed alkyne activation,[6, 7] we report herein a new approach to achieve multi-substituted triazapentalenes with high efficiency (0.5% loading, up to 96% yield, **Scheme 1B**). This new method affords a variety of TAPZ derivatives (gram-scale in some cases). Moreover, the introduction of electron-withdrawing groups significantly improved the product stability, giving air and moisture stable TAPZs that could not be achieved previously.



Scheme 1. Triazapentalene zwitterions (TAPZ): new fluorophore.

As a result of our interest in using triazole ligands to adjust transition metal complex reactivity, our group reported several new methods for triazole derivatization with good regioselectivity (N-2 vs. N-1).[8] One particularly interesting method is the synthesis of propargyl triazole through Fe-catalyzed C-O bond activation of propargyl alcohols.[11a] Using this method, both N-1 and N-2 isomers can be prepared in good yields. Our initial goal was to investigate whether these readily available propargyl triazoles could be used for TAPZ synthesis, simply through the π-acid catalyzed alkyne activation (**Scheme 2A**).

Through screening of substrates and catalysts, we found that the cyclization products **3** could be obtained in excellent yield with cationic gold complexes using N-2-triazole isomers (N-1 isomer gave no products, **Scheme 2B**).[9] The problem was the poor catalyst turnover due to the formation of the stable C-Au bond in complex **3**.



Scheme 2. Triazole-alkyne cyclization as new TAPZ synthesis.

Considering that triazolium (TAZ) is a neutral ligand with a C-binding site, we realize that the TAZ is similar to the N-heterocyclic carbene (NHC) ligands. To understand the reactivity of triazolium (TAZ) complex **3**, we prepared the corresponding TAZ-gold-NHC complex. The crystal structure is shown in **Figure 1**.

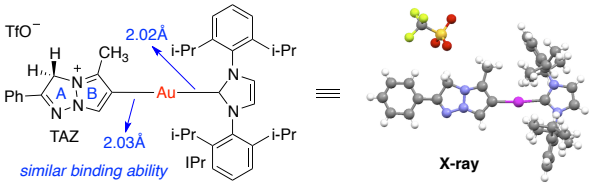
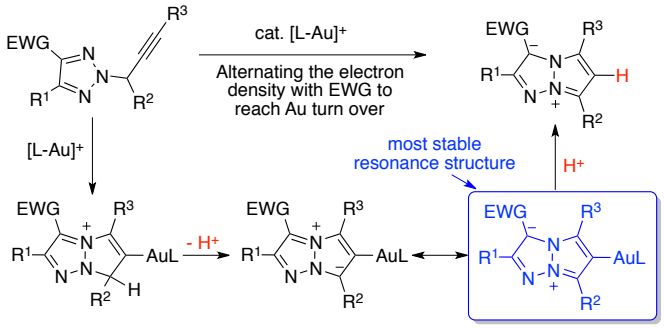


Figure 1. X-ray crystal structure of TAZ-gold-NHC complex.

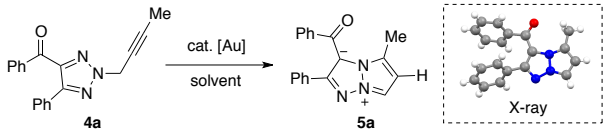
According to the X-ray crystal structures, the TAZ ligand bound to Au in a similar fashion as IPr ligand,[10] giving almost identical C-Au bond lengths. This result suggests that C-H bond in TAZ-H has similar acidity to the C-H bond in NHC-H (pKa around 21-24).[11] Considering that protonation in TAZ-Au complexes occurred on ring A instead of the C-Au bound, we postulated that the introduction of an electron-withdrawing group on ring A will reduce the basicity of the carbanion, which may "redirect" the protonation to the C-Au bond, leading to gold catalyst turnover through protodeauration, achieving TAPZ in one step (**Scheme 3**).



Scheme 3. Proposed strategy for gold turnover.

To verify our hypothesis, triazole-alkyne **4a** was prepared and charged with Au catalyst (1 mol% $PPh_3AuCl/AgOTf$). As expected, TAPZ **5a** was successfully prepared in good yield (91%) and its structure was confirmed by X-ray crystallography. Further screening (**Table 1**) revealed elevated temperature (60 °C) in DCE as the optimal conditions, giving **5a** in excellent isolated yield (96%) with only 0.5% catalyst loading.

Table 1. Optimization of reaction conditions[a,b]

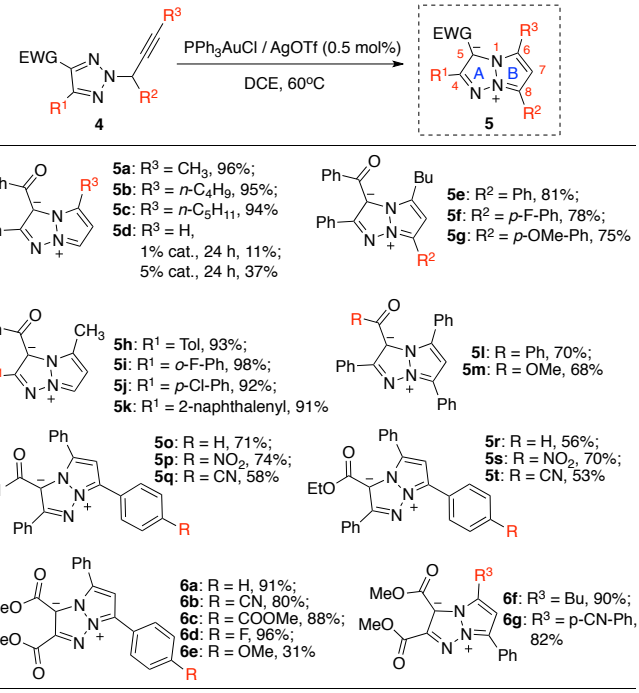


entry	catalyst	loading (%)	solvn[b]	temp (°C)	time (h)	convn (%)	yield (%)[c]
1	$AuPPh_3Cl/AgOTf$	1.0	DCM	rt	48	96	91
2	$AuPPh_3Cl/AgBF_4$	1.0	DCM	rt	48	76	72
3	$AuPPh_3Cl/AgSbF_6$	1.0	DCM	rt	48	>98	94
4	$[PPh_3Au\text{-}TA]^+TfO^-$ [e]	1.0	DCM	rt	48	69	64
5	$AuPPh_3Cl/AgSbF_6$	1.0	DCE	rt	48	>98	92
6	$AuPPh_3Cl/AgSbF_6$	1.0	THF	rt	48	75	69
7	$AuPPh_3Cl/AgSbF_6$	1.0	MeCN	rt	48	<5	-
8	$AuPPh_3Cl/AgSbF_6$	1.0	$MeNO_2$	rt	48	7	-
9	$AuPPh_3Cl/AgSbF_6$	1.0	DCE	60	3	>98	>98
10	**$AuPPh_3Cl/AgSbF_6$**	**0.5**	**DCE**	**60**	**4**	**>98**	**96[d]**
11	$AuPPh_3Cl/AgSbF_6$	0.2	DCE	60	48	79	77[d]

[a] General reaction conditions: **4a** (0.5 mmol), catalyst (0.2-1.0 mol%) in 5 mL solvent, the reactions were monitored by TLC, rt-60°C; [b] DCE: 1,2-dichloroethane; [c] NMR yields of **5a** with 1,3,5-trimethoxybenzene as internal standard; [d] Isolated yield; [e] TA = N-methyl-benzotriazole.

With the optimal conditions in hand, various N-2-alkynyl-triazoles were prepared to explore the reaction substrate scope. The results are summarized in **Table 2**.

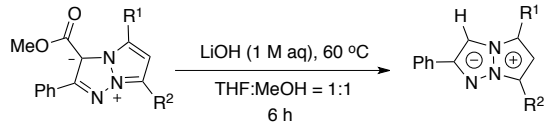
Table 2. Reaction substrate scope[a,b]



[a] Standard reaction condition: **4** (0.5 mmol), $AuPPh_3Cl/AgSbF_6$ (0.5 mol%) in DCE (5 mL), the reactions were monitored by TLC (3-24 h), 60 °C; [b] Isolated yield.

As shown in **Table 2**, this reaction tolerates a large group of substrates. Both alkyl (**5a-5c**) and aryl (**5l**) groups are suitable for the alkyne terminal, giving the corresponding TAPZ in excellent yields. The terminal alkyne (**5d**) gave poor result due to the slow reaction rate (*anti*-Markovnikov addition) and competitive gold catalyst decomposition (after long time of reaction). Besides ketone, the ester group can also be used as the EWG (**5m**) to promote the gold turnover (though with lower yields). Introducing the second ester group on C-4 position significantly increased the yields of TAPZs (**6a-6d**). Notably, the EWG-free TAPZ (reported by Namba

and Tanino),[5] although not as stable, can also be prepared using this method through a simple decaboxylation as shown in **Scheme 4**. This result greatly highlighted the versatility of this new method as a general approach for the preparation of broad scope of TAPZs.



5m : R_1 = Ph, R_2 = Ph
5n : R_1 = CH_3, R_2 = H

7m : 76% yield
7n : 68% yield

Scheme 4. Preparation of EWG-free TAPZ through decarboxylation.

As discussed above, one of our main goals is to overcome the poor stability associated with the mono-substituted TAPZs. In fact, dissolving compound **7** in untreated $CDCl_3$ caused an immediate color change from light yellow to green. To quantize the decomposition, we monitored the TAPZ solution with ^{1}H NMR over time. The C-4, C-5 di-substituted TAPZs prepared using this new method indicated significantly improved stability, giving almost no decomposition over two weeks, while the previously reported mono-substituted TAPZ **7** started to decompose within hours under the identical conditions (see NMR data in SI). With these stable ketone and ester substituted-TAPZ available, we explored their optical properties (**Figure 2**).

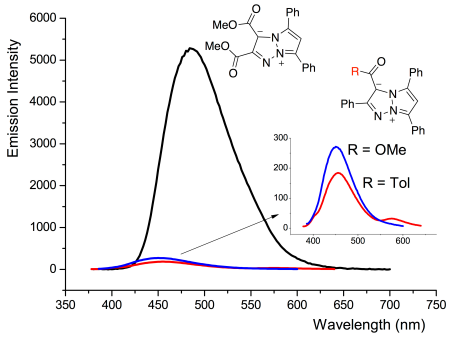


Figure 2. Emission spectra of selected TAPZs.

According to the fluorescent spectra, the diester TAPZ exhibited much stronger emission (Φ_F = 0.15) than the monoester TAPZ and ketone TAPZ (Φ_F < 0.01). These results not only confirmed the improved fluorescence properties, but also provided promising future application through the available ester "synthetic handle". The investigations on substitute-group effects toward fluorescence emissions and applications of these new dyes as selective biomarkers and/or probes (with modification on the ester groups) are currently under investigation in our group.

Conclusions

In summary, we report the investigation of gold catalyzed triazole-alkyne 5-endo-dig cyclization for the synthesis of stable triazapentalene zwitterions (TAPZs). Through the introduction of electron-withdrawing groups, the electron density distribution on the triazapentalene was altered, which resulted in effective gold catalyst turnover. Good to excellent yields of desired TAPZs were achieved in most cases. In addition, the resulting ester modified TAPZs exhibit excellent fluorescence, which highlighted great potential of this new TAPZ synthesis.

Acknowledgement

We thank NSF (CHE-0844602) and NSFC (21228204) for the financial supports. We also thank the financial support from NSF MRI on NMR instrumentation (CHE-1228336) and X-ray diffractometer (CHE-1336071)

Notes and references

[a] C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506, United Staes. Fax: 304-293-4904; Tel: 304-293-0179; E-mail: Xiaodong.Shi@mail.wvu.edu.
[b] BioNano Research Facility, West Virginia University, Morgantown, WV 26506, USA
[c] Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (MOE), School of Pharmacy, Shandong University, Jinan, Shandong, 250012, China

† Electronic Supplementary Information (ESI) available: NMR, UV fluorescence spectra and X-ray data with CCDC numbers. See DOI: 10.1039/c000000x/

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