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### Intermolecular Desymmetrizing Gold-Catalyzed Yne-Yne-Reaction of Push-Pull Diarylalkynes

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**Abstract:** Push-pull diaryl alkynes are dimerized in the presence of a cationic gold catalyst. The polarized structure of the applied starting materials enables the generation of a highly reactive vinyl cation intermediate in an intermolecular reaction. Trapping of the vinyl cation by a nucleophilic attack of the electron-poor aryl unit then leads to the selective formation of highly substituted naphthalenes in a single step and in complete atom economy.

In the field of gold catalysis<sup>[1]</sup> reactions in which diyne systems are applied as starting materials are becoming increasingly importance.<sup>[2]</sup> While this development began with cascade reactions in which one alkyne unit is transformed into a nucleophilic part as relay for further transformations,<sup>[3]</sup> only recently direct reactions between two

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intermediates such as, gold vinylidenes,<sup>[4]</sup> diaurated phenyl cations,<sup>[5]</sup> aurated vinyl cations<sup>[6]</sup> and aurated phenyl cations,<sup>[7]</sup> intermediates that enabled valuable downstream transformations in the corresponding catalytic cycles. So far, all of these transformations were restricted to intramolecular processes and examples for an intermolecular generation of these high energy intermediates from two reacting alkyne units via gold catalysis were unknown. If two terminal alkynes are applied as substrates for intermolecular reactions, instead of the formation of high energy intermediates, head to tail couplings are observed,<sup>[8]</sup> a well-known methodology that is not specific for gold catalysis and that is extremely prominent in the literature for a highly diverse set of metal catalysts.<sup>[9]</sup> In contrast, reactions that involve metal-catalyzed dimerizations of non-terminal alkynes are restricted to only a few examples. For example diarylalkynes can undergo a rhodium-catalyzed dimerization towards naphthalene derivatives in the presence of catalytic amounts of strong acids.<sup>[10]</sup> This process is assumed to proceed via an oxidative addition of HX onto the metal center, insertion of the alkyne into the Rh-H bond, CH-activation of the aryl-H bond followed by the insertion of the second alkyne and a subsequent reductive elimination to the products. In addition diarylalkynes are known to dimerize to azulene derivatives in the presence of Pd, but yields are generally low and high loadings or even stoichiometric amounts of metal are necessary.<sup>[11]</sup> In the presence of stoichiometric amounts of oxidant and Cu as additive, some substrates form naphthalenes in the presence of Pd catalysts, but under these conditions mainly  $8.8-\alpha$ -dihydrocyclopenta[a]indenes are obtained.<sup>[12]</sup> Gold catalysts are known to dimerize non-terminal ynamides which gives rise to cyclopentadiene derivatives in most cases.<sup>[13]</sup>

connected alkyne parts were in the focus. These systems give rise to high energy

Inspired by our recent work on the generation of vinyl cations by means of *intramolecular* alkyne-alkyne gold catalysis,<sup>[6]</sup> we envisioned that the *intermolecular* reaction of diaryl alkynes might result in the formation of an intermediate vinyl cation that, upon addition of one of the aryl units, would deliver naphthalene structures in perfect atom economy (Scheme 1). Compared to the mentioned rhodium-catalyzed protocol, a completely different mechanism would operate without a change of the oxidation state of the metal and the accompanying need for scope-limiting acidic additives that are needed for the generation of the active Rh(III) species. In addition a selective formation of the intermediate cation from differently substituted diaryl alkynes would allow access to naphthalene derivatives with alternating aryl units.



Scheme 1: Proposed gold-catalyzed process.

An initial screening for the desired reactivity was conducted with push-pull diyne 1a, a substrate that was selected due to its electronic nature, which we considered as ideal for a potential reaction towards alternating naphthalene systems. Indeed with [(IPr<sup>\*</sup>)Au(NCMe)]SbF<sub>6</sub> as catalyst, moderate yields of naphthalene **2a** were observed in  $C_6F_6$  as inert solvent. Switching the counter ion to BArF<sub>24</sub> (which turned out to be the ideal counter ion for the intermolecular generation of phenyl cations)<sup>[7]</sup> delivered only poor results. Changing the solvent to DCE turned out to be beneficial and a high yield of 78% was obtained after one day with the SbF<sub>6</sub><sup>-</sup> counter anion. Attempts to lower the temperature to 80°C were unsuccessful and only incomplete conversions were obtained, even after prolonged reaction times. A short ligand screening revealed that the sterically bulky IPr\* ligand<sup>[14]</sup> has to be favored to the smaller IPr ligand or JohnPhos as representative for a Buchwald-type ligand. Finally, the reaction was conducted in at higher concentration. In addition to a higher reaction rate, the yield of 89% turned out to be significantly better. In order to establish the connectivity of the obtained naphthalene scaffold, single crystals of 2a were grown and analyzed by Xray diffraction.<sup>[15]</sup> The substitution pattern of the exclusively obtained product 2a can be rationalized by the proposed mechanistic scenario (Scheme 1) combined with the intrinsic polarity of the applied alkyne. The selectivity of the nucleophilic attack of the alkyne is controlled by the stability of the intermediate cation, while the attack only takes place at the more electrophilic position at the second alkyne which is activated by the gold catalyst bound to the more nucleophilic carbon (Scheme 2). Based on this interplay, alternating substituents can be selectively placed at the central naphthalene core. In contrast, the control reaction with the Rh catalyst system introduced by Miura's group, in an unselective reaction delivered only 32% of product 2a, accompanied by regioisomer 2a' that was obtained in 37% (Scheme 3). This lack of selectivity can result from unselective insertions of either the alkyne into the Rh-H bond or the alkyne into the intermediate rhodacycle.

#### Table 1: Screening with Substrate 1a



Entry	Catalyst	Solvent	time	Т	conversion	yield
				[°C]		
1	[(IPr <sup>*</sup> )Au(NCMe)]SbF <sub>6</sub>	1 ml C <sub>6</sub> F <sub>6</sub>	2 d	100	100%	57% <sup>[b]</sup>
2	IPr <sup>*</sup> AuCl/NaBARF	1 ml C <sub>6</sub> F <sub>6</sub>	5 d	100	5%	0%
3	[(IPr <sup>*</sup> )Au(NCMe)]SbF <sub>6</sub>	1 ml DCE	1 d	100	100%	78% <sup>[b]</sup>
4	[(IPr <sup>*</sup> )Au(NCMe)]SbF <sub>6</sub>	1 ml DCE	5 d	80	56%	47%
5	[(IPr)Au(NCMe)]SbF <sub>6</sub>	1 ml DCE	5 d	100	42%	29%
6	[(JohnPhos)Au(NCMe)]SbF6	1 ml DCE	5 d	100	18%	0%
7	[(IPr <sup>*</sup> )Au(NCMe)]SbF <sub>6</sub>	0.1 ml	16 h	100	100%	89% <sup>[b]</sup>
		DCE				

[a] Reactions were run in a 250 μmol scale. Yields were determined by <sup>1</sup>H NMR spectroscopy, hexamethylbenzene was used as an internal standard if not otherwise noted. [b] isolated yield.



[(IPr\*)Au(NCMe)]SbF<sub>6</sub>

[(IPr)Au(NCMe)]SbF<sub>6</sub>

 $[(JohnPhos)Au(NCMe)]SbF_{6}$ 



Scheme 2. Left: Solid state molecular structure of 2a; right: model to explain the obtained selectivity.



Scheme 3: Rhodium-catalyzed transformation of 1a

After this optimization of the conditions, we focused on the scope of the dimerization reaction (Table 2). Besides the CF<sub>3</sub>-group as electron withdrawing substituent (2a), ester (2b), ketone (2c), triflate (2d) and halide moieties (2e) were tolerated well and the corresponding products could be obtained in moderate to good yields. The latter two deserve a special note as these are potential building blocks for further derivatizations using cross coupling strategies. The tolerance of these groups can be explained by the low tendency of the gold catalyst against oxidative addition. As a next step, the electron-rich part of the diarylalkyne was varied. An unprotected phenolic hydroxyl group was also tolerated well (2f). Higher substituted aryl groups were also suitable (2f-2g), but a slight drop in yield was observed for starting materials 1i bearing one of the methoxy groups in *ortho*-position, which can be rationalized by sterical hindrance. Electron-rich heterocyclic systems like different thienyl groups (2j, 2k) afforded the desired products in moderate yield, too. However, the indole substrate 1p showed an unexpected reactivity. In this case the more nucleophilic carbon C3 of the indole attacks the  $\pi$ -activated triple bond, which ultimately leads to the formation of Nmethylcarbazole derivative **3p** (Scheme 4). If instead of an electron-donating aryl unit,

alkyl groups such as cyclohexyl or *tert*-butyl groups (**1**I, **1m**) were used, no reaction was observed, which can be rationalized by the much lower stabilization of an intermediate vinyl cation. Tolanes with decreased polarization of the alkyne (**1n**, **1o**) gave a complex product mixture.

#### Table 2: Substrate scope



limitations:

1p

CF<sub>3</sub>

3p, 57%

![](_page_8_Figure_2.jpeg)

![](_page_8_Figure_3.jpeg)

Scheme 4: Dimerization of indole substrate 1p

In conclusion, an efficient gold-catalyzed protocol for the synthesis of highly substituted naphthalene derivatives is presented. A cationic gold complex enables the generation of a highly reactive vinyl cation in an intermolecular reaction of two diaryl alkynes. The method allows to build up complex polyaromatic structures in a single step from readily available starting materials. Mechanistically, the methodology is orthogonal to known strategies catalyzed by other transition metals, which not only enables a systematic permutation of the substituents at the naphthalene core, but also allows the installation of halide atoms for potential further transformations. Additional studies on the exploitation of intermolecular gold-catalyzed alkyne dimerization are ongoing in our laboratories.

#### References

[1] a) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* 2016, *45*, 1331-1367; b) R.
Dorel, A. M. Echavarren, *Chem. Rev.* 2015, *115*, 9028-9072; c) H. Ohno, *Isr. J.*

*Chem.* **2013**, *53*, 869-882; d) N. Bongers, N. Krause, *Angew. Chem. Int. Ed.* **2008**, *47*, 2178-2181; *Angew. Chem.* **2008**, *120*, 2208-2211; e) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449; *Angew. Chem.* **2007**, *119*, 3478-3519; f) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936; *Angew. Chem.* **2006**, *118*, 8064-8105.

[2] A. M. Asiri, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 4471-4503. [3] For selected contributions, see: a) N. Kim, C. Oh, A. Kim, W. Park, D. Park, Synlett 2006, 2006, 2781-2784; b) J. Zhao, C. O. Hughes, F. D. Toste, J. Am. Chem. Soc. 2006, 128, 7436-7437; c) A. Das, H. K. Chang, C. H. Yang, R. S. Liu, Org. Lett. 2008, 10, 4061-4064; d) C. Zhang, D.-M. Cui, L.-Y. Yao, B.-S. Wang, Y.-Z. Hu, T. Hayashi, J. Org. Chem. 2008, 73, 7811-7813; e) C. Sperger, A. Fiksdahl, Org. Lett. **2009**, *11*, 2449-2452; f) S. Kramer, J. L. H. Madsen, M. Rottländer, T. Skrydstrup, Org. Lett. 2010, 12, 2758-2761; g) C. A. Sperger, A. Fiksdahl, J. Org. Chem. 2010, 75, 4542-4553; h) A. S. K. Hashmi, M. Bührle, M. Wölfle, M. Rudolph, M. Wieteck, F. Rominger, W. Frey, Chem. Eur. J. 2010, 16, 9846-9854; i) K. Hirano, Y. Inaba, T. Watanabe, S. Oishi, N. Fujii, H. Ohno, Adv. Synth. Catal. 2010, 352, 368-372; j) A. S. K. Hashmi, T. Häffner, M. Rudolph, F. Rominger, Chem. Eur. J. 2011, 17, 8195-8201; k) K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii, H. Ohno, J. Org. Chem. 2011, 76, 1212-1227; I) D.-H. Zhang, L.-F. Yao, Y. Wei, M. Shi, Angew. Chem. Int. Ed. 2011, 50, 2583-2587; Angew. Chem. 2011, 123, 2631-2635; m) G. Yue, Y. Zhang, L. Fang, C.-c. Li, T. Luo, Z. Yang, Angew. Chem. Int. Ed. 2014, 53, 1837-1840; Angew. Chem. 2014, 126, 1868-1871; n) W. Rao, D. Susanti, B. J. Ayers, P. W. H. Chan, J. Am. Chem. Soc. 2015, 137, 6350-6355. [4] a) L. Ye, Y. Wang, D. H. Aue, L. Zhang, J. Am. Chem. Soc. 2012, 134, 31-34; b) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, Organometallics 2012, 31, 644-661; c) A. S. K. Hashmi, M. Wieteck, I. Braun, P. Nösel, L. Jongbloed, M. Rudolph, F. Rominger, Adv. Synth. Catal. 2012, 354, 555-562; d) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, Angew. Chem. Int. Ed. 2012, 51, 4456-4460; Angew. Chem. 2012, 124, 4532-4536; e) A. S. K. Hashmi, M. Wieteck, I. Braun, M. Rudolph, F. Rominger, Angew. Chem. Int. Ed. 2012, 51, 10633-10637; Angew. Chem. 2012, 124, 10785-10789; f) K. Graf, P. D. Hindenberg, Y. Tokimizu, S. Naoe, M. Rudolph, F. Rominger, H. Ohno, A. S. K. Hashmi, ChemCatChem 2014, 6, 199-204; g) M. H. Vilhelmsen, A. S. K. Hashmi, Chem. Eur. J. 2014, 20, 1901-1908; h) J. Bucher, T. Stößer, M. Rudolph, F. Rominger, A. S. K.

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10.1002/chem.201800360

Hashmi, Angew. Chem. Int. Ed. 2015, 54, 1666-1670; Angew. Chem. 2015, 127, 1686-1690; i) C. Yu, B. Chen, T. Zhou, Q. Tian, G. Zhang, Angew. Chem. Int. Ed. 2015, 54, 10903-10907; Angew. Chem. 2015, 127, 11053-11057.

[5] a) M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 2593-2598; *Angew. Chem.* **2013**, *125*, 2653-2659; b) Y. Wang, A. Yepremyan, S. Ghorai, R. Todd, D. H. Aue, L. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 7795-7799; *Angew. Chem.* **2013**, *125*, 7949-7953; c) M. M. Hansmann, S. Tšupova, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 2215-2223.

[6] T. Wurm, J. Bucher, S. B. Duckworth, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* 2017, *56*, 3364-3368; *Angew. Chem.* 2017, 129, 3413-3417.
[7] T. Wurm, J. Bucher, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* 2017, *359*, 1637-1642.

[8] a) S. Sun, J. Kroll, Y. Luo, L. Zhang, *Synlett* **2012**, 54-56; b) A. S. K. Hashmi, T. Lauterbach, P. Nösel, M. H. Vilhelmsen, M. Rudolph, F. Rominger, *Chem. Eur. J.* 

**2013**, *19*, 1058-1065; c) N. Endo, M. Kanaura, M. P. Schramm, T. Iwasawa, *Eur. J. Org. Chem.* **2016**, *2016*, 2514-2521; d) S. Mader, L. Molinari, M. Rudolph, F.

Rominger, A. S. K. Hashmi, Chem. Eur. J. 2015, 21, 3910-3913.

[9] S. E. García-Garrido, in *Modern Alkyne Chemistry*, Wiley-VCH, **2014**, pp. 299-334.

[10] a) L.-Y. Huang, U. R. Aulwurm, F. W. Heinemann, H. Kisch, *Eur. J. Inorg. Chem.* **1998**, *1998*, 1951-1957; b) K. Sakabe, H. Tsurugi, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 445-449.

[11] a) G. Nöll, M. Zabel, F. Hampel, E. Schmälzlin, C. Bräuchle, K. Meerholz, *Chem. Eur. J.* 2003, *9*, 4232-4239; b) E. Müller, G. Zountsas, *Chem. Ztg.* 1973, *97*, 447; c)
E. Müller, G. Zountsas, *Chem. Ztg.* 1974, *98*, 41.

[12] T.-C. Wu, C.-C. Tai, H.-C. Tiao, Y.-T. Chang, C.-C. Liu, C.-H. Li, C.-H. Huang,
M.-Y. Kuo, Y.-T. Wu, *Chem. Eur. J.* 2011, *17*, 7220-7227.

[13] S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz, T.

Skrydstrup, Angew. Chem. Int. Ed. **2011**, *50*, 5090-5094; Angew. Chem. **2011**, *123*, 5196-5200.

[14] A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5541-5543.

[15] CCDC 1572052 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

![](_page_12_Figure_3.jpeg)

**Tolan Wedding:** The *intermolecular* and selective gold-catalyzed dimerization of polarized tolan derivatives gives rise to highly substituted naphthalenes *via* reactive vinyl cation intermediates. This methodology is superior to existing unselective strategies catalyzed by other transition metals and offers an entry to naphthalenes with a controlled substitution pattern of electron-rich and electron-poor aryl groups.