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Graphical Abstract

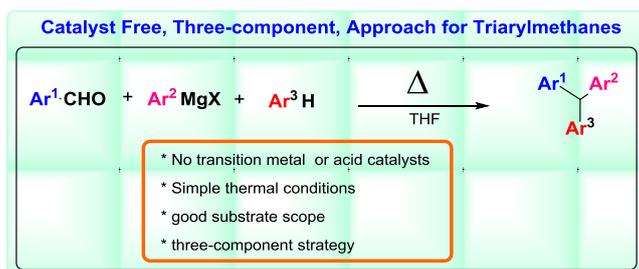
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Catalyst free, three-component approach for unsymmetrical triarylmethanes (TRAMs)

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This manuscript describes the first catalyst free, three component approach to triarylmethanes.



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ABSTRACT

An efficient catalyst free, three-component, cascade approach has been designed and developed for the rapid assembly of unsymmetrical triarylmethane framework. The strategy employed aromatic aldehydes, Grignard reagents, and neutral aromatics as reaction partners, under simple thermal conditions. This process affords very broad scope for all three partners as it is performed in the absence of any external additives.
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The development of synthetic methodologies for quick assembly of complex molecules with biological and material importance is of great interest from synthetic, environment and economical point of view. Therefore, recently tremendous efforts have been directed towards the discovery and development of efficient atom- and step-economical synthetic methods.¹ Multicomponent, tandem strategies will provide an opportunity to rapidly generate structural complexity from simple subunits. Reagent free multicomponent reactions are highly environment friendly and observed very rarely in organic synthesis.

Triarylmethanes (TRAMs) have attracted much attention because of their unique structural and physical properties.² The triarylmethane motif has become one of the basic core structures for fluorescent molecules.³ This substructure is also finding increased application in medicinal chemistry, such as antitubercular and anticancer agents⁴ as well as potassium ion (K⁺) channel blockers.⁵ Recently, a variety of fluorescent TRAMs have been applied in live cell imaging,⁶ and several TRAMs bearing metal binding sites are employed as selective sensors for metal ions.⁷ Thus, it is becoming increasingly important to have efficient synthesis routes to symmetrical as well as unsymmetrical triarylmethanes.

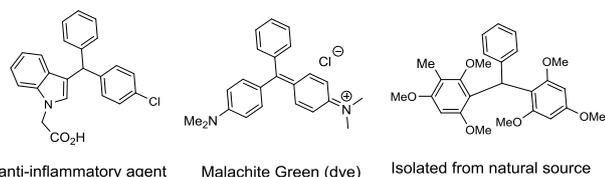
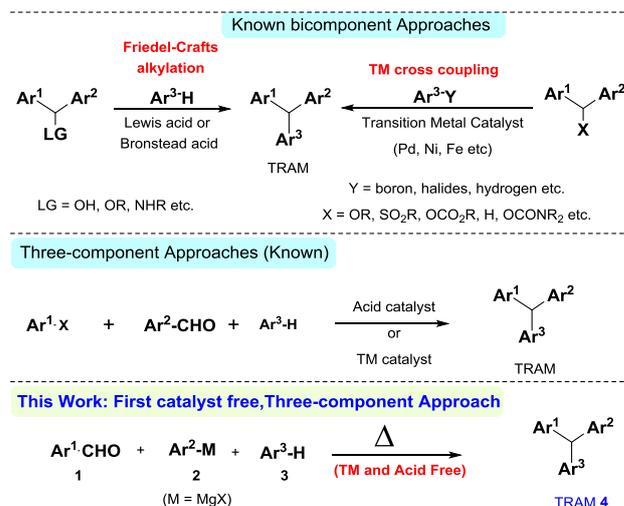


Figure 1. Representative triarylmethane based drugs, dyes and natural products

The Friedel–Crafts arylation, which involves the reaction between diarylmethanol or related derivatives and arenes in the presence of an acid catalyst is one of the most employed methods for the synthesis of triarylmethanes.^{8,9} Recently, transition metal-promoted coupling strategies have emerged as an alternative methods to provide access to structurally divergent triarylmethane frameworks.¹⁰ But, both these strategies have a common feature among them i.e., the catalyst promoted condensation between a mono-aryl unit and a di-arylmethane derivative.

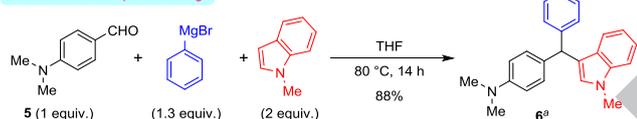


Scheme 1. A) Known strategies (bi- and three-component) for the synthesis of TRAMs; and B) our catalyst free, three-component, cascade approach.

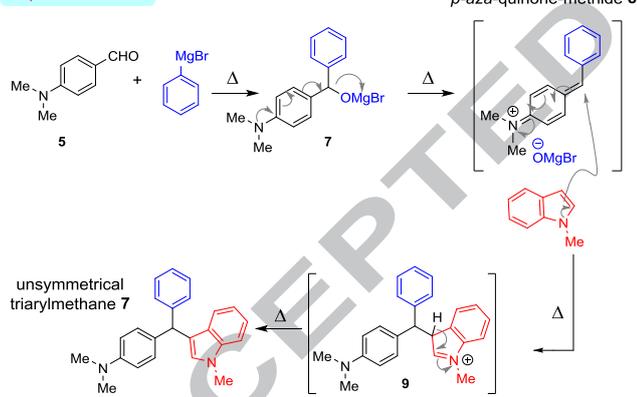
Several reports¹¹ appeared on the synthesis of triarylmethanes from three mono-aryl units. But all these methods employ either acid catalysts or transition metal catalysts. Here in, we report for the first time an acid and transition metal free, three-component domino strategy for the rapid generation of unsymmetrical triarylmethanes by employing simple thermal conditions. According to our designed strategy, an aromatic aldehyde **1** ($\text{Ar}^1\text{-CHO}$) in the absence of any external reagents, would undergo a tandem, sequential nucleophilic addition by an aromatic carbanion reagent ($\text{Ar}^2\text{-M}$, $\text{M} = \text{MgX}$ or Li) **2** and a neutral aromatic nucleophile ($\text{Ar}^3\text{-H}$) **3**, under thermal heating to generate the triarylmethane derivative **4**.

To test our hypothesis, initially we have treated 4-(*N,N*-dimethyl)benzaldehyde **5**, with PhMgBr (1.3 equiv.) in presence of *N*-Me-indole (2 equiv.) in THF (Scheme 2). To our delight, the expected TRAM **6** was formed in 88% yield after heating the reaction mixture at 80 °C for 14 h. Formation of **6** can be explained as a two stage cascade process (Scheme 2). First the Grignard addition to the aldehyde **5** to give the magnesium diarylcarbinoloxide **7**, followed by nucleophilic trapping of the in situ generated *p*-azaquinone-methide intermediate **8** by the aromatic nucleophile and re-aromatization of iminium ion **9** affords TRAM **7**. Encouraged by this result, we next performed this transformation at various temperatures 55 °C and 100 °C, but none of them afforded better yields.

Execution of tricomponent design:



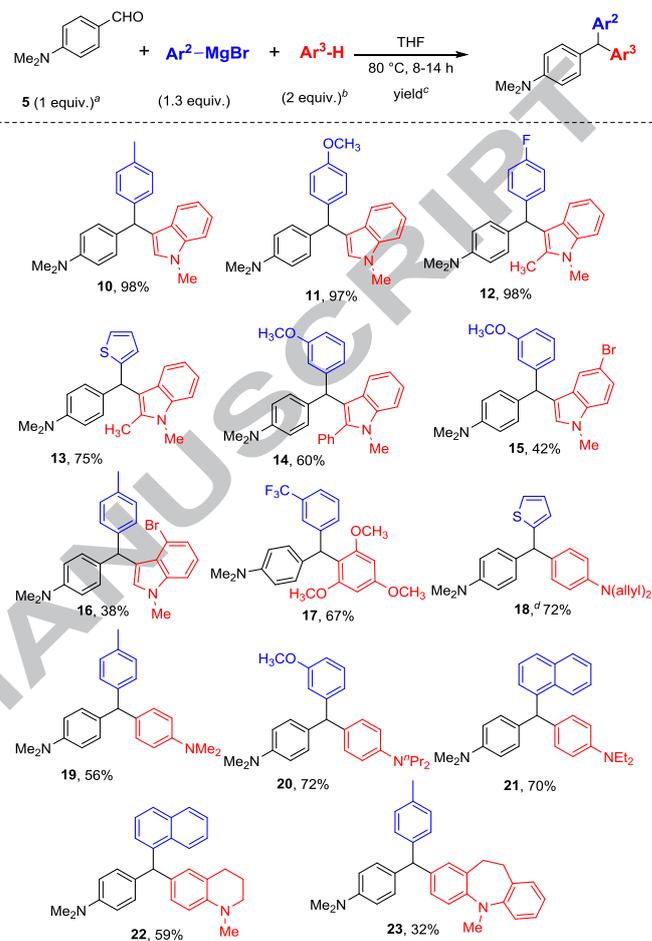
Proposed Mechanism:



Scheme 2. A) Preliminary investigation on the designed three-component approach for the synthesis of triarylmethanes; and B) Possible mechanism. a) When, we employed PhLi in place of PhMgBr , the reaction was very slow and even after 50 h at 80 °C only 23% of TRAM **6** was isolated along with 32% of the alcohol **6'** (see supporting information for details)

Next we performed a substrate scope study for various ArMgX reagents as well as for neutral aromatic nucleophiles (Scheme 3) keeping the aldehyde **5** as the primary substrate. Initially, diversely functionalized and substituted ArMgX reagents, such as 2-thienyl, 1-naphthyl, *p*-toluyl, *m*- and *p*-anisyl, *m*- CF_3 -phenyl-, *p*- F -phenyl etc., were employed in combination with various substituted indoles, to quickly generate structurally divergent and complex unsymmetrical TRAM derivatives **10-17**. In continuation, *N*-substituted anilines were also employed as neutral aromatic nucleophiles along with variety of aromatic Grignard reagents. All these nucleophiles very smoothly underwent the three-component domino reaction for the rapid generation of corresponding unsymmetrical triarylmethanes **18-21** in good yields.

Bicyclic and tricyclic anilines were also used as efficient nucleophiles to afford TRAMs **22** and **23** in good yields. It is worth notifying here that, all the anilines were exclusively acted as nucleophiles through *para*-position. There was no detection of isomeric *ortho*- nucleophilic addition product.

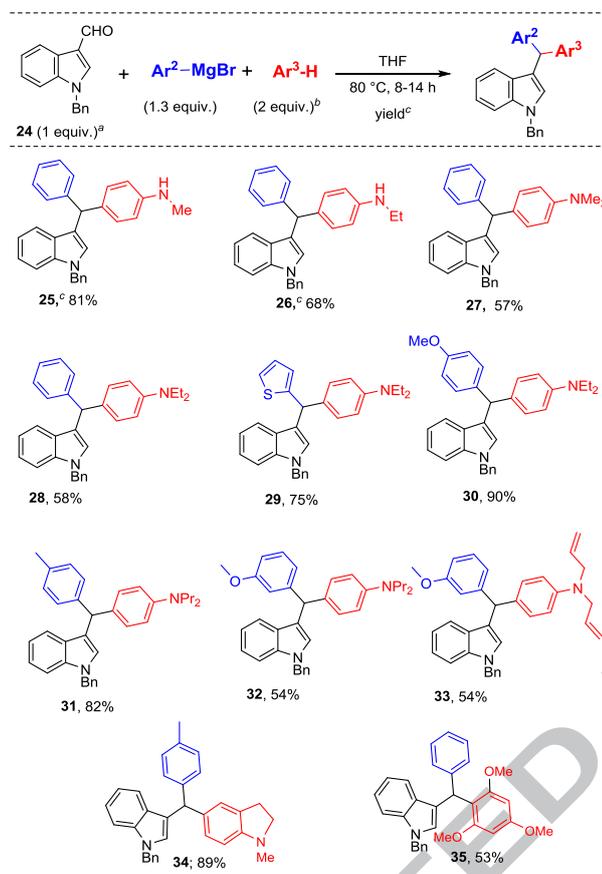


Scheme 3. Scope study for Grignard reagents and aromatic nucleophiles with *p*-(dimethylamino)benzaldehyde. a) reagents and conditions: aldehydes = 50 mg, RMgX (1.3 equiv.), Ar-H (2 equiv.); 80 °C; b) ~1 equivalent of excess Ar-H was recovered in all cases; c) yields after chromatographic purification; d) When, we employed 2-thienylLi in place of 2-thienylMgBr, the reaction was very slow and even after 50 h at 80 °C only 13% of TRAM **18** was isolated along with 52% of the alcohol **18'** (see supporting information for details)

Furthermore, we planned to employ indole-3-carbaldehyde¹¹ **24** as the aldehyde component along with various aromatic Grignard reagents and aniline derivatives as neutral nucleophiles (Scheme 4). Different *N*-substituted (*mono*- as well as *di*-) aniline derivatives afforded structurally divergent, variously colored unsymmetrical TRAMs **25-35** in variable yields under thermal heating conditions at 80 °C.

After developing a novel cascade strategy for the rapid synthesis of TRAMs, we next envisioned an opportunity for the generation of interesting monoaryl-bisindolylmethanes by employing this methodology (Scheme 5). Accordingly, when we carried out the reaction with aldehyde **24** and PhMgBr , in presence of 2 equivalents of *N*-Me-indole at RT, there formed as expected hetero-BIM **37** but the reaction was very slow (3 days, 57%). But to our delight at 60 °C, formation of hetero-BIM **37** was faster (20 h) and efficient (65%). Encouraged by this result, we next investigated a scope study for various indoles to generate the structurally diverse monoaryl-BIMs. *N*-Me-indole as well as

N-benzyl-indole nucleophiles leads to the exclusive formation of **37-40** and **37**, **41-43** in good yields respectively. Simple indole as the nucleophile gave the hetero-BIM **44**, and it was further utilized to generate functionalized hetero-BIMs **45-47**, employing sodium hydride (NaH) mediated alkylation with various functionalized electrophiles like allyl bromide, ethyl bromoacetate, and bromo-ethanol.



Scheme 4. Scope study for Grignard reagents and aromatic nucleophiles with indole-3-carbaldehydes. a) reagents and conditions: aldehydes (50 mg), RMgX (1.3 equiv.), Ar-H (2 equiv.), $80\text{ }^\circ\text{C}$; b) ~ 1 equivalent of excess Ar-H was recovered in all cases; c) yields after chromatographic purification

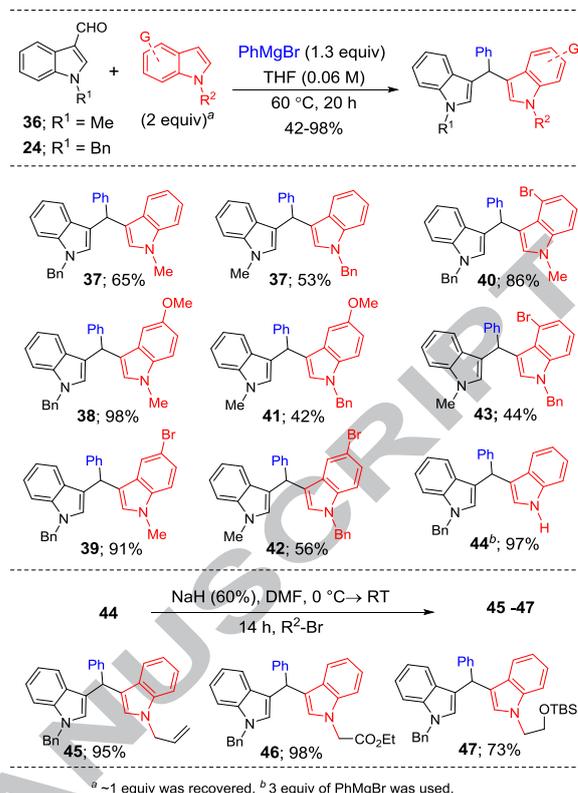
In summary, we have developed an efficient, catalyst free, three-component, domino approach for the rapid assembly of unsymmetrical triarylmethanes. We employed aromatic aldehydes, Grignard reagents, and neutral aromatics as reaction partners, under simple thermal conditions. This process affords very broad scope for all three partners as it is performed under the absence of any external additives.

Acknowledgments

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Supplementary Material

Supplementary data (^1H , ^{13}C NMR spectra for all new synthesized compounds and experimental procedures) (PDF) associated with this article can be found in the online version, at [http:// dx.doi.org/xxxxxxx](http://dx.doi.org/xxxxxxx).



Scheme 5. Rapid access to functionalized monoaryl-bisindolylmethanes

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Salient features of our strategy are:

- First acid and transition metal free strategy to TRAMS
- Simple thermal conditions and highly efficient
- Three-component, tandem approach
- Very broad substrate scope

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