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Triarylmethyl Cation-Catalyzed Three-Component Coupling for the Synthesis of Unsymmetrical Bisindolylmethanes

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Abstract: An efficient synthesis of unsymmetrical bisindolylmethanes has been accomplished using triarylmethyl cations to catalyze the reaction of *N*-arylimines with two different indoles. Optimization of the organocatalyst by tuning cation stability allows for excellent single addition selectivity when coupled with *p*-nitrophenyl imines. The optimal catalyst is commercially available, and the reaction minimizes waste and environmental impact by employing a one-to-one ratio of starting materials. The intermediates can be isolated or used *in situ* in a one-pot two-step reaction to generate unsymmetrical bisindolylmethanes in high yields. The reaction tolerates a broad range of imines with the highest yields observed for electron-poor and neutral imines. A wide range of indole nucleophiles are also successfully employed allowing for the creation of a large variety of unsymmetrical bisindolylmethanes.

Triarylmethyl (trityl) cations are Lewis acid organocatalysts with tunable reactivity.[1] Structural changes on the aromatic rings allow for an extremely wide variation of cation stability and thus catalyst reactivity (Figure 1). Although trityl cations were first employed as catalysts decades ago,[2] they have only recently received renewed interest and development due to their exceptional tunability and lowered environmental impact as compared to more highly toxic, expensive, and/or sensitive metal-based Lewis acids.[3]

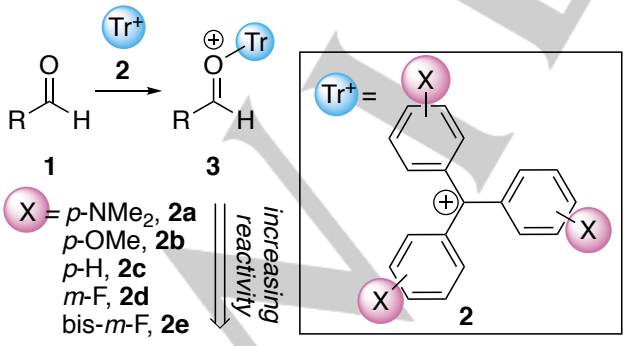


Figure 1. Trityl cations are tunable Lewis acid electrophile activators.

Recently we reported that trityl cations are exceptional catalysts for the synthesis of bisindolylmethanes via aldehyde activation (Figure 1), and the tunability of these catalysts can be exploited to tailor the catalyst to less reactive substrates.[4] The products of this reaction are symmetrical bisindolylmethanes that incorporate two identical indole units. Given the important biological activities of bisindolylmethanes, particularly their antibiotic and antitumor activities,[5] the ability to control the identity of the two indole units would be a powerful methodology to generate more diverse structures.[6] Methods for the construction of unsymmetrical bisindolylmethanes typically involve step-wise introduction of each of the aromatic rings to reach the target molecule,[7] while direct coupling methods[8] are much less developed and limitations with regard to the structure of the products remains an issue. Notably, Esquivias et. al. described the use of sulfonyl imines for a copper-catalyzed one-pot aza-Friedel-Crafts reaction.[8a] In our previous work on the synthesis of symmetric

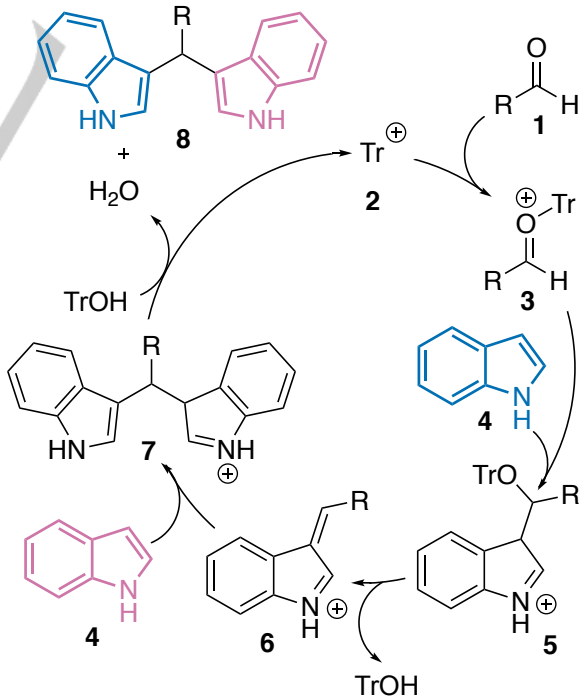
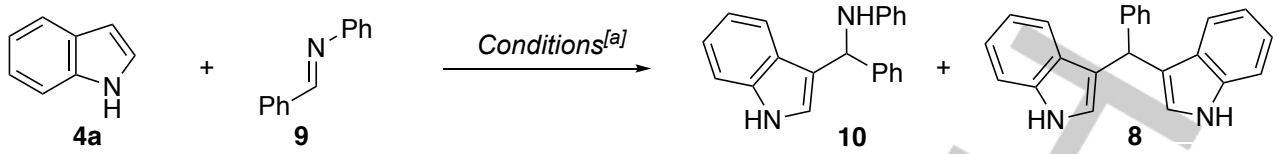


Figure 2. The proposed catalytic cycle for symmetric bisindolylmethane synthesis using a trityl catalyst (**2** = **2b** or malachite green **2f**) suggests that decreasing leaving group ability would allow for build-up of single addition intermediates, enabling unsymmetrical product formation.

Table 1. Optimization of the Single Addition of Indole **4a** to *N*-Phenyl Imine **9**.



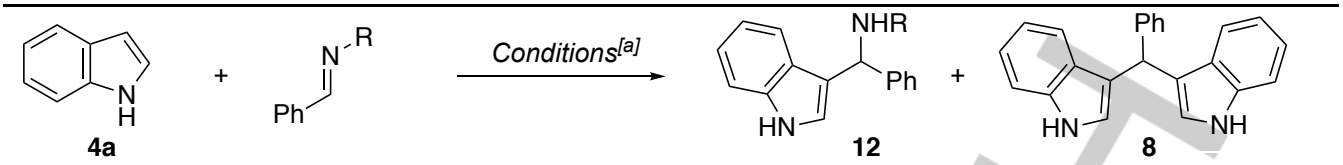
4a **9** **10** **8**

Entry	Ratio **4a**:**9**	Temperature	Catalyst	Solvent	Conversion[b]	**10**:**8**	Yield **10**[b]
1[c]	1:2	0 ºC	10 mol% Ph_3CBF_4 **2c**	DCM	100%	0:1	0%
2	1:2	0 ºC	10 mol% HBF_4	DCM	100%	0.05:1	5%
3	1:2	0 ºC	10 mol% (*p*-$OMeC_6H_4)_3CBF_4$ **2b**	DCM	100%	0.09:1	8%
4	1:2	0 ºC	10 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	DCM	100%	1.6:1	61%
5	1:2	RT	10 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	DCM	100%	0.6:1	38%
6	1:2	RT	10 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	MeCN	100%	4.5:1	82%
7[d]	1:2	0 ºC	10 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	MeCN	82%	14:1	77%
8	1:2	0 ºC	10 mol% (*p*-$NMe_2C_6H_4)_2PhCCl$ **2f**	MeCN	100%	5:1	83%
9	1:2	RT	5 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	MeCN	89%	2:1	59%
10[d]	1:1	RT	5 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	MeCN	93%	1.7:1	59%
11	1:1	RT	10 mol% (*p*-$NMe_2C_6H_4)_3CCl$ **2a**	MeCN	100%	1.9:1	66%

[a] Imine **9** (26.0 mg, 0.14 mmol) in solvent added to catalyst in solvent, followed by indole **4a** in solvent (0.1M) at 0 ºC or RT. Reaction stirred for 14 hours. [b] Determined by ^{1}H NMR integration. [c] Color disappeared upon addition of imine **9**. [d] Reaction time was 3 days.

bisindolylmethanes, no buildup of an intermediate mono-addition product was observed, which we attributed to the propensity of these intermediates to expel they tritylated leaving group (Figure 2). Employing imines rather than aldehydes would allow for accumulation of an intermediate by decreasing leaving group ability, thus allowing us to intercept the intermediate with a different nucleophile to create an unsymmetrical product.[9] Additionally, because trityl catalysts are highly tunable through manipulation of the electronics of the aromatic rings (Figure 1), we can optimize the catalyst structure to maximize intermediate formation over symmetric bisindolylmethane production. We began our investigations using indole **4a** and phenyl imine **9** as substrates (Table 1). To favor single addition product **10**, indole **4a** was used as the limiting reagent with imine **9** in a two-fold excess. Employing the simplest trityl catalyst, triphenylmethyl cation **2c**, gave full conversion, but only the double-addition product was observed (Entry 1). Upon addition of the imine, the yellow color of the trityl catalyst disappeared, indicating that the catalyst was not being turned over in the reaction. The active catalyst is synthesized by addition of fluoroboric acid to a triarylmethyl alcohol pre-catalyst. Omitting the pre-catalyst and using only fluoroboric acid produced a very small amount of the single addition product (Entry 2). Given the catalyst quenching observed, the reactivity of the catalyst appeared to be too high, so we next turned to the less activated catalyst trimethoxy cation **2b**. This gave an improved 8% yield of the desired single addition product (Entry 3). Further catalyst tuning indicated that cation **2a**, commercially available as the chloride salt crystal violet, favored the single addition product **10** over the undesired double addition product **8** in a 1.6:1 ratio (Entry 4). This catalyst is a dye used in biological staining and is inexpensive and readily available. At ambient temperature this ratio was decreased to 0.6:1 (Entry 5). Changing the solvent to acetonitrile improved the ratio to 4.5:1 (Entry 6). This solvent is much less harmful to the environment as compared to dichloromethane, so this improvement was particularly fortuitous. Lowering the temperature to 0 ºC improved this ratio to 14:1, at the expense of reaction rate (Entry 7). Three days were necessary to achieve 83% conversion. Despite the improved ratio, the overall yield of the single addition productdropped to 77% due to this decreased conversion. Increasing the catalyst activity by removing one of the dimethylamino groups increased reactivity but decreased selectivity to 5:1 (Entry 8). Decreasing the catalyst loading had a detrimental effect on both conversion and selectivity (Entry 6 vs. Entry 9). Encouragingly, decreasing the amount of imine employed to give a more ideal 1:1 ratio gave only a slight decrease in selectivity (Entry 10). Increasing the catalyst loading led to improved reactivity and slightly improved selectivity. To increase reactivity while maintaining selectivity, we turned to tuning the imine identity (Table 2). Changing the phenyl group to p-chlorophenyl imine **11** had a slightly negative effect on selectivity (Entry 2 vs. Entry 1). Fortunately, switching to p-nitrophenyl imine **13a** gave improved selectivity (Entry 4). Notably, the p-nitrophenyl imine was not entirely dissolved in the reaction mixture. Cooling the reaction had a detrimental effect on the conversion (Entry 5). Unexpectedly, decreasing the catalyst loading improved conversion (Entry 6). This change also improved selectivity to 9.2:1. Decreasing the ratio of the two substrates to the ideal 1:1 ratio had a very small impact on the

Table 2. Optimization of Imine **11** to Improve Reactivity and Selectivity.



Entry	Ratio **4a**: imine	Temperature	R	Mol% **2a**	Conversion[b]	**12**:**8**	Yield **12**[b]
1	1:2	RT	Ph **9**	10%	100%	4.5:1	82%
2	1:2	RT	*p*-ClC_6H_4 **11**	10%	100%	4.3:1	81%
3[c]	1:2	RT	*p*-$NO_2C_6H_4$ **13a**	10%	100%	8:1	89%
4[c]	1:2	0 ºC	*p*-$NO_2C_6H_4$ **13a**	10%	73%	2.4:1	52%
5[c]	1:2	0 ºC	*p*-$NO_2C_6H_4$ **13a**	5%	100%	9.2:1	91%
6[c]	1:1	0 ºC	*p*-$NO_2C_6H_4$ **13a**	5%	100%	9:1	90%
7[c]	1:1	RT	*p*-$NO_2C_6H_4$ **13a**	5%	100%	3.1:1	76%

[a] Imine, indole **4a**, and crystal violet were dissolved in acetonitrile (0.1M) at 0 ºC or RT. Reaction stirred for 14 hours. [b] Determined by ^{1}H NMR integration. [c] Imine **13a** was not entirely soluble.

selectivity and yield, which allowed us to use this more optimal ratio. This also provided the opportunity to directly use the intermediate formed, since little starting materials remained to interact with a second nucleophile upon introduction. Increasing the temperature had a detrimental effect (Entry 7).

The solubility of different *p*-nitrophenyl imines vary with structure, thus concentration and temperature were optimized for individual substrates. Two concentrations (0.1 and 0.05M) and three temperatures (RT, 0, and -20 ºC) were screened for each imine to optimize the yield of each intermediate (Scheme 1). The catalyst loading was kept constant at 5 mol %. The parent phenyl imine **13a** provided adduct **14a** in 91% isolated yield. Electron-poor substrates such as the *p*-chloro imine **13b** and the *p*-cyano imine **13c** were excellent substrates, giving 97% and 91% yield respectively. *p*-Cyano imine **13c** is less soluble than other substrates, and more dilute conditions were found to be beneficial in such cases. Electron-rich substrates required lower temperatures to achieve high yields due to poorer selectivity at higher temperatures. *p*-Methyl adduct **14d** was obtained in 85% yield at -20 ºC. *p*-Methoxyphenyl imine **13e** was too unreactive at -20 ºC to carry out the reaction in a reasonable time-period. The reaction was therefore done at 0 ºC and gave moderate selectivity, resulting in 76% yield. *p*-Thiomethylphenyl imine **13f** was sufficiently reactive, allowing for the reaction to be carried out at -20 ºC. This improved selectivity, providing single addition product **14f** in 82% yield. *o*-Pyridine imine **13g** was slow to react, likely due to interaction with the catalyst, and therefore required a higher temperature for the reaction to occur. The selectivity was still excellent at this temperature, however, resulting in 91% yield of the *o*-pyridine adduct **14g**. Ortho-substitution such as that present in *o*-tolyl imine **13h** was tolerated, however the adduct **14h** was obtained in only 64% yield, which is lower than other substitution patterns. The indole could also be varied to produce adducts with functionalized indole groups such as 5-methoxyindole adduct **14i**, which was obtained in 95% yield. Alkylation of the nitrogen was also tolerated, providing isopropyl adduct **14j** in 83% yield. 2-Methyl indole was an excellent substrate, yielding single addition adduct **14k** in 95% isolated yield when the reaction was carried out at -20 ºC. Interestingly, 3-methyl indole did participate in the reaction at the C2 position, albeit with a lower yield of 50%.

These results indicate that in general, electron-poor substrates give the highest yields, but even electron-rich and sterically hindered substrates give useful yields under these conditions. Tuning the temperature and concentration was needed to achieve high yields for all substrates, but this optimization led to some general observations that allow us to make predictions for new substrates. For electron-poor imines, more dilute conditions are superior. Electron-rich substrates give poorer selectivity and should therefore be carried out at the lowest temperature that still provides adequate reaction rate to obtain high yields. Substrates that are poorly reactive, such as the pyridine imine **13g**, which may compete for trityl-binding, or reactions employing less reactive indoles such as 3-methylindole **4l**, must be done at slightly higher temperatures to achieve satisfactory reaction rates.

Fortunately, the high selectivity of pyridine imine **13g** results in a high yield of the corresponding adduct **14g**. Estimating the activity of new substrates allows one to make an informed approximation for the best conditions and thereby avoid screening multiple conditions for each new substrate.

With the optimization of the first addition step complete, we turned our attention to the development of a one-pot, two step reaction

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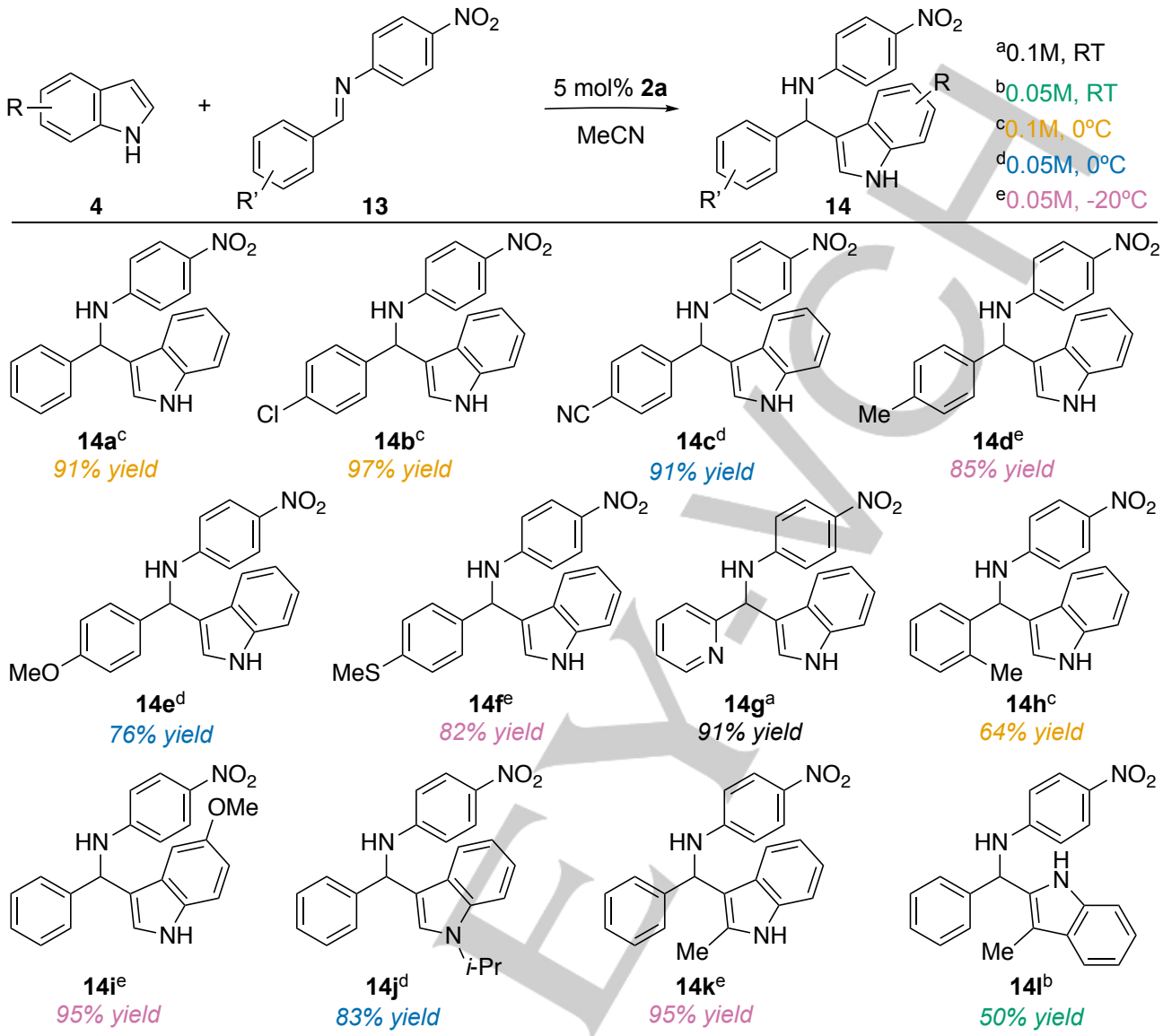

Scheme 1. Substrate scope of the crystal violet-catalyzed indole addition to imines. Imine **13** (1 mmol), indole **4** (1 mmol), and crystal violet **2a** (0.05 mmol), dissolved in acetonitrile was stirred for 14 hours. [a] RT. [b] Concentration was 0.1M, 0 ºC. [c] Concentration was 0.05M, 0 ºC. [d] Concentration was 0.1M, -20 ºC. [e] Concentration was 0.05M, -20 ºC. [f] Concentration was 0.1M [g] Concentration was 0.05M.

sequence to generate non-symmetric bisindolylmethanes **15** (Scheme 2). The first step of the sequence was done using the indole nucleophile expected to give the highest yield of intermediate **13**, then the second indole was added in a slight excess (1.2 equivalents) and the reaction was driven to completion by an increase in temperature to 80 ºC. For example, unsymmetrical bisindolylmethane **15a** containing one *N*-isopropyl indole and one indole unit was obtained in 71% yield in the one-pot sequence when indole **4a** was used as the first nucleophile. When *N*-isopropyl indole **4j** was used as the first nucleophile, the yield was decreased to 60%, reflecting the lower yield of the initial step to form intermediate **14j** as compared to **14a**. For imines or indoles not employed previously, such as 5-methylester indole **4b**, an assessment of the likely reactivity was made according to the trends observed during the screening process. In this case, the more electron-poor indole was expected to be both less reactive and more selective in comparison to indole **4a** and was therefore likely to give a higher yield of intermediate **14**. This was confirmed by the event: when 5-methylester indole **4b** was employed as the first nucleophile, the unsymmetrical bisindolylmethane **15b** was obtained in 87% yield, while employing indole **4a** as the first nucleophile gave a reduced 70% yield of isolated product. Interestingly, this trend did not hold true in the case of 5-methoxy indole **4i**. Unsymmetrical bisindolylmethane **15c** was isolated in 70% yield when 5-methoxy indole **4i** was the first nucleophile, but in an improved 85% yield when indole **4a** was added first. This was imputed to a less successful second step due to the decreased reactivity of the intermediate and a poorer nucleophile in the second step. *N*-Alkylated indoles generally gave slightly lower selectivities in the first step when compared to other indoles tested. We wondered which order of addition would give the highest yield when an electron-rich indole such as methoxy indole

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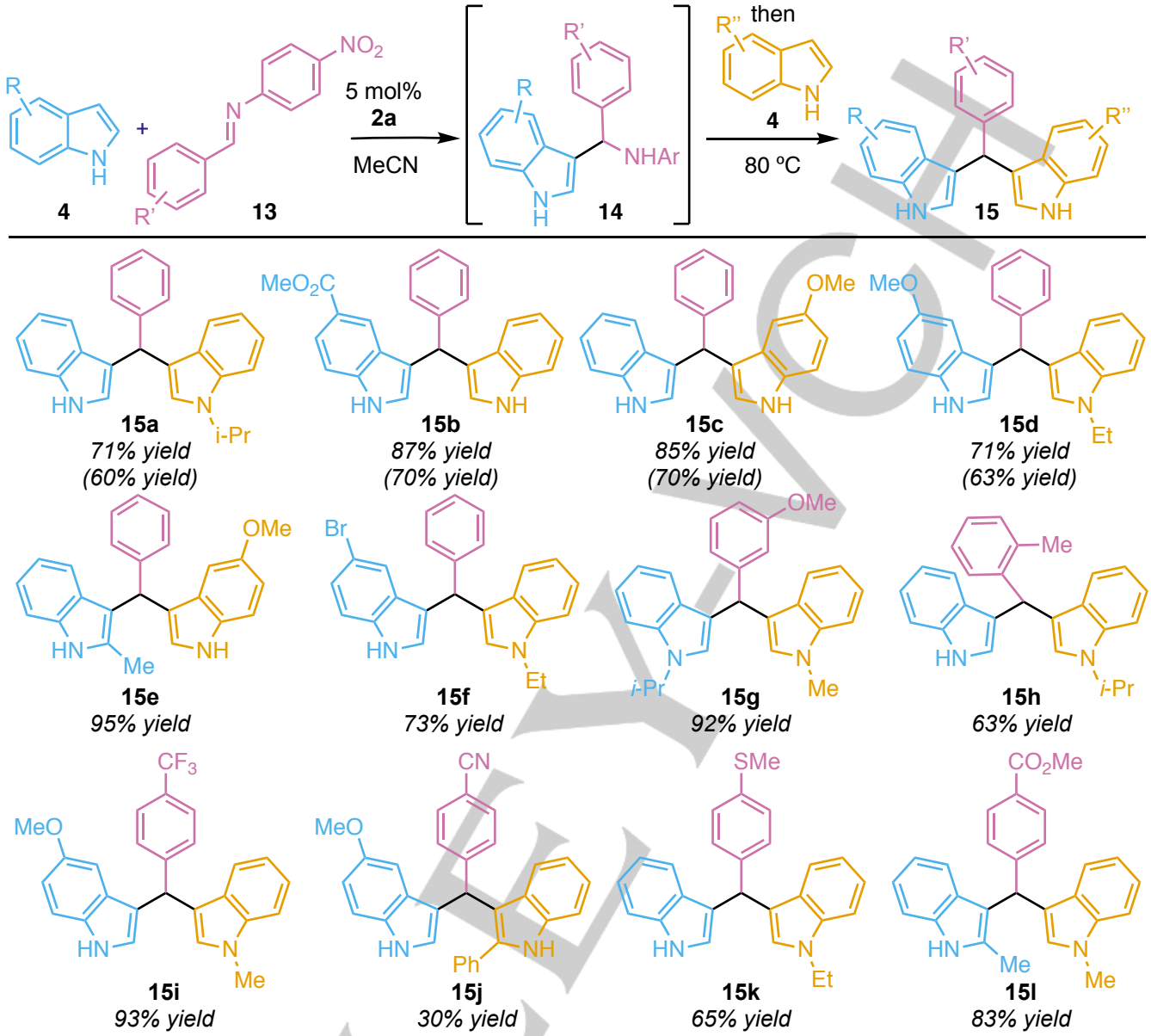

Scheme 2. One-pot two-step synthesis of bisindolylmethanes catalyzed by crystal violet. Imine **13** (1 mmol), indole **4** (1 mmol), and crystal violet **2a** (0.05 mmol), dissolved in acetonitrile was stirred for 14 hours. The second indole was then added and the reaction was heated to 80 ºC. Yields in parentheses are for switching the order of addition of the two indoles.

4i was used in combination with a less selective indole such as *N*-ethyl indole **4d**. In the event, adding methoxy indole **4i** as the first nucleophile outperformed using the less selective *N*-ethyl indole as the initial nucleophile for the synthesis of unsymmetrical bisindolylmethane **15d**. The difference in yields, 71% and 63% respectively, was much less than when the more highly selective indole **4a** was used (8% difference versus 15% difference). When electron-poor imines were used, such as *p*-trifluoromethyl imine **13n** for the synthesis of bisindolylmethane **15i**, methoxy indole **4i** could be used as the first nucleophile without detrimental impacts to the yield (93% yield), presumably due to the increased reactivity of the intermediate due to the electron-withdrawing group present.

A variety of indoles **4** and imines **13** were reacted to generate a wide variety of unsymmetrical bisindolylmethanes **15** with electron-rich, neutral, and electron-poor ring systems at each of the three aromatic rings. All indoles tested in the second addition step were found to be compatible, giving high to moderate yields with a similar trend as had been observed for the single addition products. As expected, the best results were achieved for combinations in which the individual components gave high yields in the single addition reactions. For example, bisindolylmethane **15e** was obtained in 95% yield after the two-step, one-pot protocol. Phenyl imine **13a** reacts with high selectivity with both 2-methyl indole **4k** and 5-methoxy indole **4i**, in line with the results for the one-pot methodology. On the other hand, bisindolylmethane **15h** was obtained in only 63% yield, likely due to the combination of

the sterically hindered *o*-tolyl imine **13h** and *N*-isopropyl indole **4j**, both of which gave lower than average yields in the initial addition step. Although this yield is rather low in comparison to other combinations tested, bisindolylmethane **15h** is still formed in useful amounts, and this sterically hindered structure would be difficult to obtain by alternate means, particularly in a one-pot operation. Electron-rich imines, such as p-thiomethyl imine **13f**, gave comparably poor yields of unsymmetrical bisindolylmethanes **15k** in the one-pot reaction, presumably due to the lower reactivity of the intermediate, as was seen in the case of using 5-methoxy indole **4i** as the first nucleophile in the synthesis of bisindolylmethane **15c**. Employing a sterically hindered second nucleophile, such as 2-phenyl indole gave 30% yield of bisindolylmethane **15j**, likely due to insufficient reactivity. When employing imines not previously examined in the one-pot protocol, such as imine *p*-methoxyester **13o**, conditions were chosen based on similarity to those studied in the first step. For *p*-methoxyester **13o**, the conditions used for electron-poor **13b** were selected, giving bisindolylmethane **15l** in 83% overall yield without optimization. It is noteworthy that this protocol is applicable to bisindolylmethanes containing two unalkylated indoles as well as two differentially alkylated indoles, as these products are challenging to access by alternate methodologies.[8c-f]

Mechanistically this reaction appears to occur through a similar pathway as that proposed for the trityl-catalyzed reaction of aldehydes with indoles (Figure 2). NMR data show significant peak shifts upon addition of crystal violet to imine **13a** (see Supporting Information). The catalyst also appears to be involved in the second step as a significant drop in reactivity is observed when intermediate **14a** undergoes the second addition in the absence of catalyst (see Supporting Information).

In conclusion, the synthesis of unsymmetric bisindolylmethanes has been achieved by trityl catalysis of sequential indole additions to *p*-nitrophenyl imine electrophiles. Tuning of the imine reactivity and the catalyst gave high selectivity for the single addition step with a one-to-one stoichiometric ratio of the two substrates. This ideal ratio allowed for the development of a one-pot two-step synthesis of unsymmetrical bisindolylmethanes in which all three components could be independently varied to give moderate to high yields of the desired bisindolylmethanes **15**. Ongoing studies are aimed at evaluating these novel bisindolylmethanes for their biological activity.

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Keywords: aromatic substitution • bisindolylmethanes • carbocations • Lewis acids • organocatalysis

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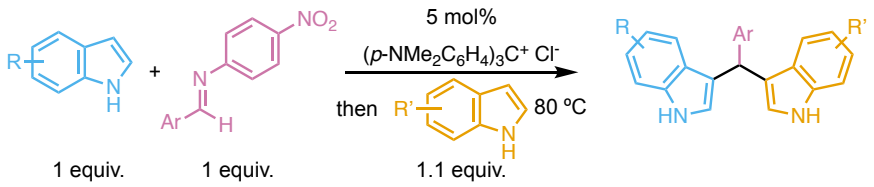

Triarylmethyl cations catalyze the synthesis of unsymmetrical bisindolylmethanes from imines and two different indoles. Optimization of the catalyst by tuning cation stability allows for excellent single addition selectivity. The single addition intermediates can be isolated or used *in situ* in a high-yielding one-pot two-step reaction to generate unsymmetrical bisindolylmethanes.

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