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N-Arylation of DABCO with Diaryliodonium Salts: General Synthesis of *N*-Aryl-DABCO Salts as Precursors for 1,4-Disubstituted Piperazines

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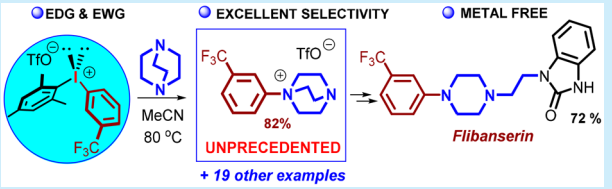
Supporting Information

ABSTRACT: Employing DABCO as a substrate, aryl(mesityl)-iodonium triflates are introduced as arylating agents for a tertiary sp^3-nitrogen. Mild conditions and exceptional selectivity of the aryl group transfer allow unprecedented *N*-aryl-DABCO salts to be obtained, bearing substituents of different electronic natures. This metal-free methodology has no analogy among known transition-metal-based reactions. The utility of isolated *N*-aryl-DABCO salts is demonstrated for the preparation of flibanserin.



N-Arylation of primary and secondary amines is the most widely applicable strategy for preparing substituted aromatic amines in modern chemistry (Figure 1). To effect this

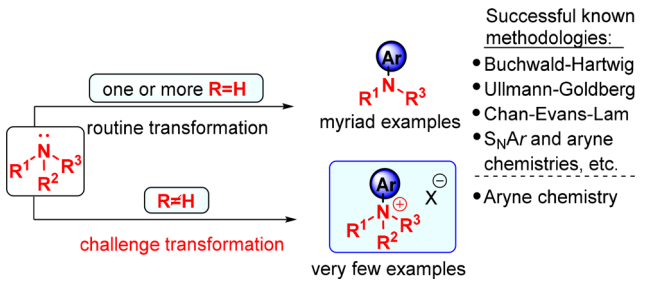


Figure 1. State of the art in arylation of an sp^3-nitrogen.

transformation, currently several methodologies exist based on employing either metal-catalyzed or metal-free reactions.[1] Almost all of these methodologies, however, routinely fail to produce quaternary N-arylated ammonium salts by the N-arylation of tertiary alkylamines. This is usually attributed to low stability of the quaternary ammonium salts toward both bases and nucleophiles, which results in dealkylation with formation of the corresponding tertiary amines instead.[1g,2a]

There are only very few examples of N-arylation of tertiary alkylamines that have successfully produced the quaternary ammonium salts, and in all of these cases, arynes are employed as aryl sources.[1g,2a,b] As is typical of aryne chemistry, this methodology suffers from low availability of specific benzyne precursors and, more significantly, substantial structural limitations. Specifically, employing most of the monofunctionalized benzynes, it is impossible to obtain 1,2-disubstituted products, whereas 1,4-disubstituted products could be prepared only as a mixture with 1,3-isomers.[2b,c] Given the wide abundance of the tertiary alkylamine functionality in natural products and pharmaceuticals as well as the importance of quaternary ammonium salts in many fields, alternative synthetic tools to convert the former into the latter which would circumvent the above issues are highly desired.

In our study aimed to fill the above gap in modern arylation methods, we chose highly nucleophilic 1,4-diazobicyclo[2.2.2]-octane (DABCO) as a model substrate to start with. Here, we present a general method for the N-arylation of DABCO, providing the first preparative access to the hitherto elusive DABCO-derived quaternary ammonium salts.[2a,3] Previous attempts to obtain them using S_NAr or aryne chemistry were unsuccessful; the initially formed salts rapidly underwent a ring opening under the reaction conditions employed.[3,4] At the same time, a few examples of their generation and in situ ring-opening reactions with nucleophiles have been recently reported, including by our group.[5] Such reactions could serve a basis for a rapid and modular synthesis of 1,4-disubstituted *N*-arylpiperazines (vide infra), which represent a common structural motif in many pharmaceuticals (Figure 2).[6] Current synthetic routes toward *N*-arylpiperazines are typically multistep and suffer from several shortcomings. They are commonly based on cyclization with anilines or transition-metal-catalyzed C_{aryl}−N bond-forming reactions.[7] High costs of catalysts and possibility of toxic metal contaminations in the end products represent serious practical concerns for the latter, whereas the former requires harsh reactions conditions. As such, a general and widely applicable method for the preparation of quaternary *N*-aryl-DABCO salts as precursors for 1,4-disubstituted piperazines represents a practically important, yet challenging, task.

To address the task above, we elected to employ diaryliodonium salts as an arylating agent. Owing to their good reactivity, low toxicity, and moisture and air stability, these compounds have been experiencing a growing

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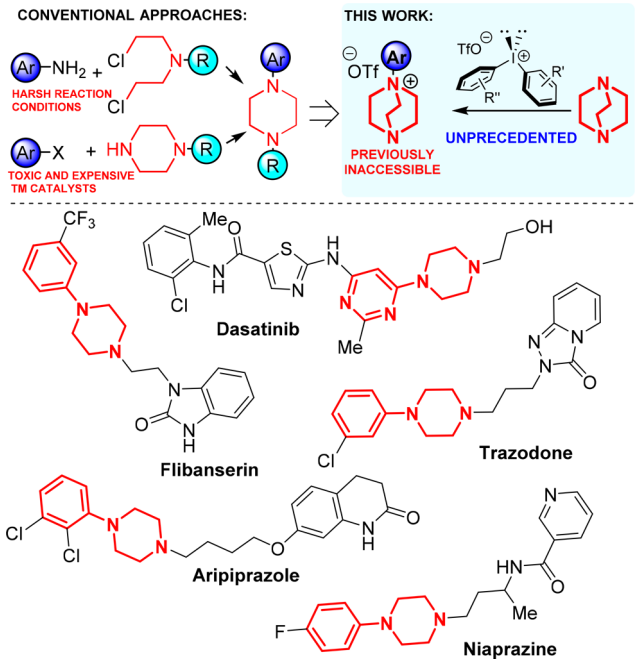
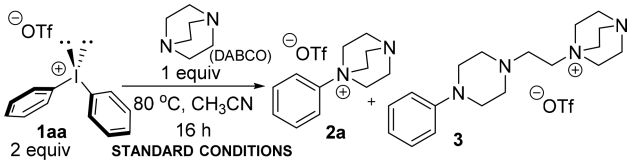


Figure 2. 1,4-Disubstituted *N*-arylpiperazines: Synthetic approaches and selected pharmaceutical agents.

Table 1. Optimization of the Reaction Conditions[a]



entry	deviations from the standard conditions	ratio[b] 2a/3	yield (%)[c] 2a + 3
1	none	100:0	98 (94)[d]
2	1 equiv of **1aa**, 7 h	90:10	67
3	1.2 equiv of **1aa**	87:13	68
4	1.5 equiv of **1aa**	94:6	83
5	1 equiv of **1aa**, EtOAc	89:11	68
6	1 equiv of **1aa**, CH_3NO_2	81:19	63
7	DMF, 25 °C or DMSO, 60 °C	<39:61	>93
8	PhCl, 120 °C	100:0	75
9	DCE, THF, H_2O, MeOH, EtOH, PhMe or *c*-hexane	82:18−100:0	5−49

[a]Reactions conditions: DABCO (0.25 mmol, 1 equiv) in 2.5 mL of solvent. [b]Molar ratios calculated by integration of ^{1}H NMR spectra of the crude reaction mixture. [c]^{1}H NMR yields using 2,5-dibromo-*p*-xylene as an internal standard. The stated values are the sum of ^{1}H NMR yields of individual compounds present in the crude reaction mixture. [d]Isolated yield.

application in organic synthesis as reagents for selective arylation of diverse nucleophiles under metal-free or metal-catalyzed conditions.[1c,e,8,9] Moreover, the recently developed synthetic routes to these reagents in batch[8] and continuous-flow[10] have made them easily available in a safe and scalable manner at low cost. Metal-free reactions of diaryliodonium salts are of special interest to the pharmaceutical industry as they offer a solution to the problem of toxic metal contaminants being present in the ultimate products.[8b] Arylation of primary and secondary amines with diaryliodonium salts in a metal-free manner pioneered by Beringer and co-workers[11a] in the early 1950s has been extensively developed recently into a powerful synthetic methodology by the groups of Stuart[9j] and Olofsson.[9p] However, arylation of a tertiary sp^3-nitrogen atom employing the same type of reagents has been exemplified only by the reaction of Ph_2IBF_4 and Me_3N under drastic reaction conditions reported by Nesmeyanov in 1957.[11b]

Our investigations began with examination of the reaction of DABCO with Ph_2IOTf (**1aa**) under different conditions (Table 1). Considering the previous research,[3] we anticipated that, owing to the high reactivity of **2a** toward nucleophiles, the formation of **3**, arising from a nucleophilic attack of DABCO on the initially formed **2a**, could represent a significant problem. To our delight, however, the expected **2a** was formed in nearly quantitative yield and excellent chemoselectivity when the reaction was performed in MeCN with 2 equiv of **1aa** at 80 °C. Remarkably, under these conditions, neither **3** nor the diarylated DABCO were detected (entry 1). Overall, the solvent and the ratio of reagents are crucial for the reaction to proceed with high efficiency.[6] Thus, the unprecedented salt **2a** is readily obtained in 94% isolated yield by the direct N-phenylation of DABCO with **1aa** using operationally simple procedure under catalyst- and additive-free conditions and with no special precautions to exclude air and moisture.

While the reaction optimization was carried out on the symmetrical iodonium salt **1aa**, the resulting conditions were then applied to aryl(mesityl)iodonium triflates having diverse electronic and steric effects (Scheme 1). Unsymmetrical salts are especially attractive as arylating agents because they are easier to obtain and less wasteful in the subsequent arylation than their symmetrical counterparts.[8,12] The key challenge related to using unsymmetrical diaryliodonium salts, however, is the selectivity of the aryl group transfer that is controlled sterically and electronically.[12] In our transformation, replacement of the symmetrical **1aa** by the unsymmetrical phenyl(mesityl)iodonium triflate (**1a**) led to an identical outcome with the exclusive formation of **2a** under standard conditions. For N-arylation of sterically demanded DABCO with **1a**, for which electronic effects of the aryl groups are relatively close, steric effects are the dominant factors, providing the exceptional transfer of the phenyl group rather than the bulky mesityl group (anti-ortho-effect).[12]

Having established the optimal reaction conditions and revealed the fact that the mesityl group is the effective auxiliary in **1a**, we next explored the scope of the process with respect to substituted aryl(mesityl)iodonium triflates (Scheme 1). The method showed the excellent generality for iodonium salts bearing electronically diverse substituents. *N*-Aryl-DABCO salts with both electron-withdrawing (**2e**, **2i**−**p**) and electron-donating (**2b**−**d**, **2q**, **2r**) groups in different positions of the aryl substituent were isolated in good to excellent yields. The selectivity of the reaction is guided by the steric effects, affording only the N-arylation product. Aryls with substituents of different electronic nature are exclusively transferred to the nitrogen atom, while the sterically congested mesityl serves as a "dummy" group in all cases.

Different substituents, including synthetically useful functional groups, namely halides (**2f**−**h**), ethers (**2q**, **2r**), enolizable ketone (**2i**), ester (**2j**), primary (**2m**) and tertiary (**2k**) amides, nitrile (**2l**), trifluoromethyl (**2e**, **2r**, **2s**), nitro (**2n**−**p**), and methyl (**2b**−**d**, **2p**) are viable under the standard conditions, providing, in some cases, a handle for further synthetic elaborations. (4-Methoxyphenyl)(mesityl)iodonium

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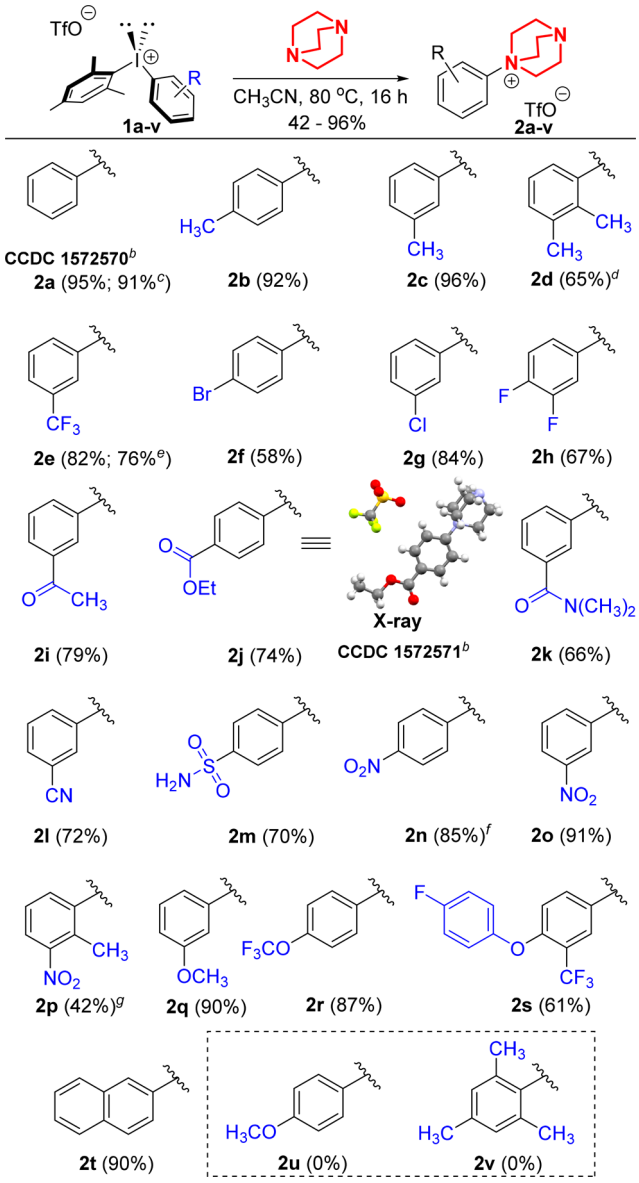
Scheme 1. Scope of Aryl(mesityl)iodonium Triflates 1[a]



[a]Reaction conditions: DABCO (0.25 mmol, 1 equiv), **1a–v** (0.5 mmol, 2 equiv) in 2.5 mL of solvent. Isolated yields. [b]For XRD data, see SI [c]Performed on 1.17 g (10.42 mmol) DABCO. [d]In PhCl at 120 °C for 12 h. [e]Performed on 467 mg (4.16 mmol) DABCO [f](4-$NO_2C_6H_4$)PhIOTf was used. [g]For 45 h.

triflate (**1u**) was unproductive despite our attempts to alter reaction conditions, whereas the less electron-donating 4-CF_3O– (**2r**) and 4-(4-FC_6H_4)O– groups (**2s**) were perfectly compatible with the process. Salts with *ortho*-substituted aryls **2d** and **2p** were formed in 65% and 42% yields. Di(mesityl)-iodonium triflate (**1v**), however, did not undergo the process even under forcing conditions.

The high effectivity of the mesityl auxiliary is an attractive feature of this transformation. Although other bulky aryl substituents are known,[13] the mesityl group is the simplest and easiest to incorporate into iodonium salts via one-pot procedures utilizing relatively inexpensive commercially available reagents.[6,8]

This highly selective reaction does not require chromatographic purification, which could be tedious in this case; analytically pure materials were isolated after a simple workup. Notably, iodomesitylene which forms as the byproduct as well as an excess of **1** can be easily recovered and reused in the subsequent reactions. The salts **2** are slightly hygroscopic crystalline compounds that can be stored at ambient conditions with no signs of decomposition. Importantly, ammonium salts in Scheme 1 have never been prepared and isolated previously and are inaccessible through current methods based on the classical S_NAr and aryne chemistries (vide supra).

Based on the experiments and the literature precedence,[6] we propose that the reaction between DABCO and **1aa** most likely proceeds via an initial formation of **A**, followed by a concerted ligand coupling at the iodine center[8] (Figure 3). According to X-ray analysis, in the isolated crystalline intermediate **A** the iodine center adopts a tetracoordinated planar arrangement with an N···I bond length of 2.848 Å.[6]

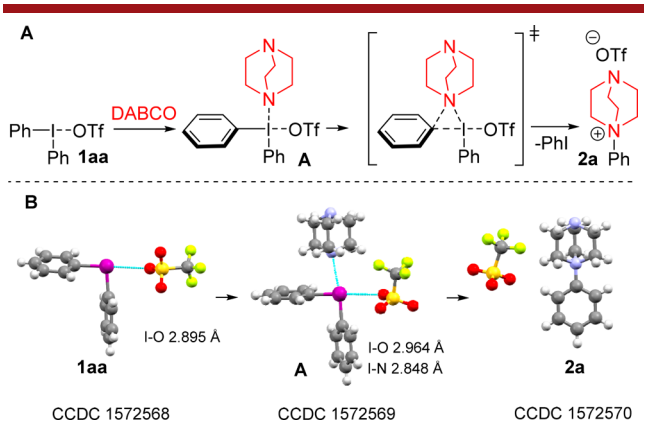


Figure 3. Plausible pathway for the formation of **2a** via a concerted ligand coupling at the iodine center and X-ray structures of **1aa**, **A**, and **2a**. (For X-ray crystallographic data, see the SI.)

With newly synthesized and isolated compounds in hand, we explored their potential with respect to the synthesis of a library of compounds. The salts **2** reacted smoothly with a variety of nucleophiles via a ring-opening pathway, delivering 1,4-disubstituted piperazines **4** in good to high yields (Scheme 2). Among the compounds prepared, **4f**, **4j**, and **4p** are known for their bioactivity.[6] The operationally simple protocol allows to introduce many important functionalities, which are common in druglike molecules (**4b**, **4e–k**, **4m**, **4o**), ligands (**4n**), and/or synthetically useful (**4a**, **4c**, **4d**, **4i**, **4l**, **4p–r**) compounds. Importantly, the reaction of **2a** with CsF provides easy introduction of the 2-fluoroethyl moiety (**4o**) and can serve as a new tool for the nucleophilic fluorination.[14] Notably, preparation of compounds **4** in Scheme 2, employing the synthetic methods reported to date, would require multistep sequences including protection/deprotection and transition-metal-catalyzed amination.[6]

To further demonstrate the synthetic applicability of **2** in the preparation of 1,4-disubstituted piperazines, we used a sequence which includes an initial alkylation of **2a** to obtain diammonium salt **5**. The subsequent reaction of **5** with $Na_2S_2O_3$[7d] resulted in deethylenation to afford piperazine **6** in good yield (Scheme 3A). In contrast to the examples in Scheme 2, in this case, one of three ethylenes plays a role of a "built-in" protective group for a step-economical preparation of 1,4-disubstituted piperazines. The salt **3**, easily prepared by the

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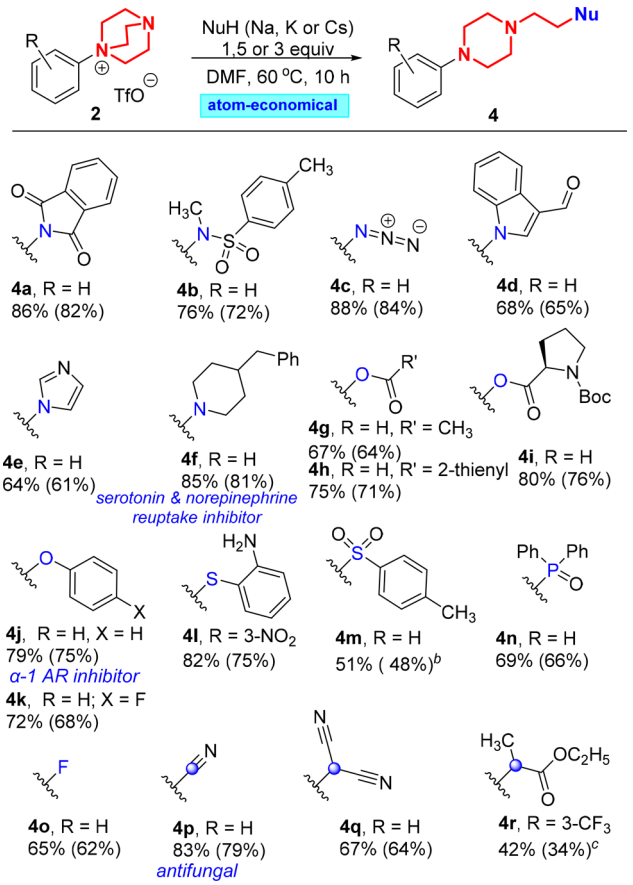
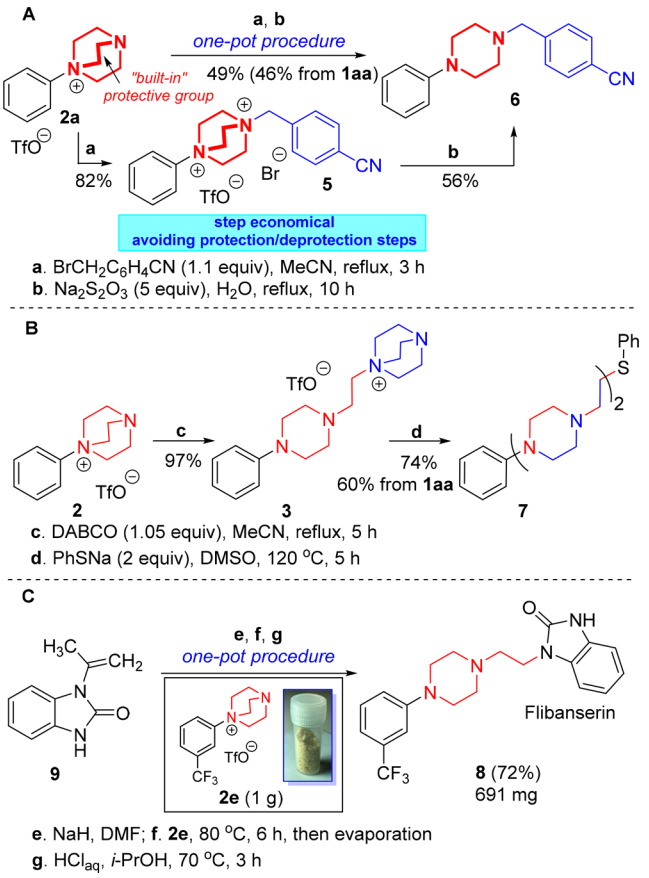
Scheme 2. Reaction Salts 2 with Nucleophiles[a]



[a]For details, see the SI. Yields calculated over two steps from **1** are shown in parentheses. [b]Sodium *p*-toluenesulfinate was used. [c]Sodium ethyl 2-methy-3-oxobutanoate was used.

Scheme 3. Synthetic Applications of Salts 2



reaction **2a** and DABCO, also undergoes the ring-opening with PhSNa to form bis-piperazine **7**. Notably, reactions of **3** and **5** with nucleophiles proceed with an exclusive cleavage of the endocyclic C−N-bond; no products of the nucleophilic displacement of DABCO-moiety were detected (Scheme 3B).

Finally, further application of the synthetic value of salts **2** is demonstrated by a new, short, one-pot approach to flibaserin (**8**),[15] the active agent of recently approved drug Addyi. Employing **2e** in the reaction with the sodium salt of commercially available 1-isoprenylbenzimidazol-2-on (**9**) and subsequent deprotection gave **8** in good yield (Scheme 3C). For comparison, previously established syntheses of **8** require at least four steps and use a Pd-catalyzed amination step or toxic alkylating agents.[6]

In summary, we have developed the first synthetic approach to quaternary *N*-aryl-DABCO salts based on the arylation of a tertiary sp^3-nitrogen atom with aryl(mesityl)iodonium triflates. This highly selective transformation enables us to introduce aryl groups of different electronic natures, tolerates a wide range of functionalities, and allows the isolation of elusive, sensitive quaternary *N*-arylammonium salts in high yield and purity. The protocol illustrates the use of diaryliodonium salts with nucleophiles where other amination methods are limited or unproductive. This strategy provides a streamlined and modular approach toward piperazine scaffolds as exemplified by the concise preparation of flibanserin. We anticipate that our findings will contribute to the further exploitation of this novel methodology by medicinal and process chemists. The expansion of this first generally successful sp^3-N-arylation strategy to other tertiary amines is currently in progress in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02676.

Additional optimization data, mechanistic considerations, detailed experimental procedures, characterization data, and NMR and IR spectra (PDF)

Accession Codes

CCDC 1572568−1572571 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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