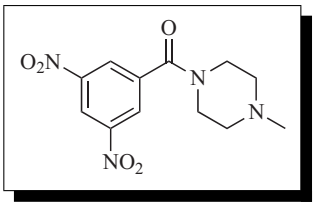
1-(3,5-Dinitrobenzoyl)-4-methylpiperazine



[67023-03-4] $C_{12}H_{14}N_4O_5$ (MW 294.26)

InChI = 1S/C12H14N4O5/c1-13-2-4-14(5-3-13)12(17)9-6-10(15(18)19)8-11(7-9)16(20)21/h6-8H,2-5H2,1H3

InChIKey = QJXVCACSGJSKAR-UHFFFAOYSA-N

(used as an oxidant in reactions where new carbon–carbon bonds are formed by the oxidation of preformed organocuprates)

Physical Data: mp 138–141 °C.

Solubility: sol dichloromethane and THF.

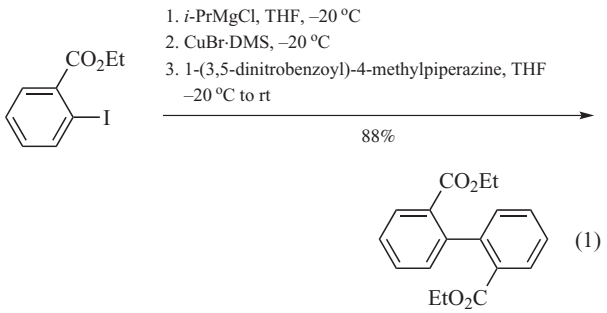
Preparative Method: 1-methylpiperazine (2.11 mL, 1.90 g, 19.0 mmol) was added dropwise to a stirred solution of 3,5-dinitrobenzoyl chloride (4.61 g, 20.0 mmol) in dichloromethane (110 mL) at 0 °C. After a further 5 min at this temperature, the reaction mixture was diluted with hydrochloric acid (2 M aqueous, 50 mL) and the aqueous layer separated, neutralized with aqueous sodium carbonate solution, and extracted with dichloromethane (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallization from hexanes to give 1-(3,5-dinitrobenzoyl)-4-methylpiperazine (3.364 g, 60%) as yellow needles.

Purification: recrystallization from hexanes.

Handling, Storage, and Precautions: store in dark container at room temperature; keep container tightly closed. Under these conditions, the reagent is bench stable and storable for years. Avoid contact with skin and eyes.

Oxidation of Organocuprates. Organocuprates are typically generated from halide-substituted precursors by halogen–metal exchange followed by transmetalation with a copper(I) source or from nonhalogenated substrates by directed lithiation followed by transmetalation.[1,2] The formation of carbon–carbon bonds by the oxidation of preformed organocuprates has proven useful in a range of synthetic contexts.[1–3] A wide variety of oxidants have been employed in such processes; some of the most common examples include oxygen gas, copper(II) salts, and nitroaromatic compounds such as 1,3-dinitrobenzene.[1,2] However, no one oxidant has shown truly broad synthetic utility. From an industrial perspective, some of the oxidants typically employed in the organocuprate oxidation processes present problems. The use of oxygen with ethereal solvents would not be countenanced on large scale and excess of inorganic oxidants such as copper(II) chloride generates significant waste disposal problems. The use of many organic oxidants often necessitates tedious and challenging purification procedures in order to obtain the pure product free of oxidant-derived by-products. Many nitroaromatic oxidants suffer from difficulties of toxicity, which could be especially troublesome when used in pharmaceutical manufacture unless suitable purification methods are available. The use of 1-(3,5-dinitrobenzoyl)-4-methylpiperazine as an oxidant is advantageous in this context; the presence of the tertiary amine functional group allows facile separation of products from excess oxidant and oxidant-derived by-products by an aqueous acid wash during workup or by passage of the reaction mixture through a thin pad of silica gel.[4–6]

Oxidation of Aryl Organocuprates. The oxidation of preformed aryl organocuprates allows the formation of biaryl bonds.[2,3] The intermolecular homocoupling of a range of aryl and heteroaryl cuprates using 1-(3,5-dinitrobenzoyl)-4-methylpiperazine as the oxidant has been reported.[4,6] These cuprates were generated from halide-substituted precursors by a sequence of halogen–metal exchange, either iodine–magnesium or bromide–zinc, followed by transmetalation with CuBr·DMS. Using this approach, a wide range of functionalized biaryls could be prepared.[4,6] For example, application of the organomagnesium-based cuprate protocol allowed the homocoupling of ethyl 2-iodobenzoate (eq 1)[4] and the organozinc-based coupling protocol was utilized to homocouple 2-bromothiophene (eq 2).[6]



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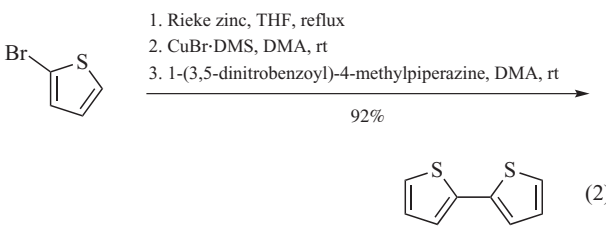
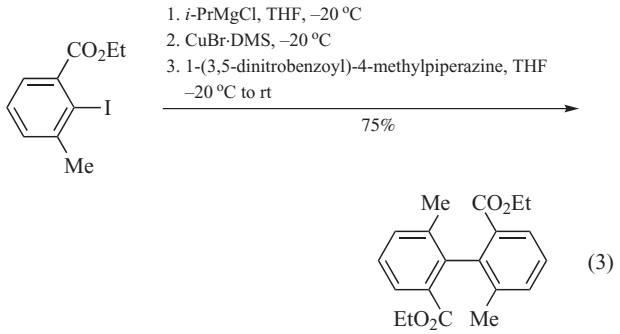


(2)

These coupling reactions were not significantly affected by steric interactions, which allowed the synthesis of biaryl bonds with multiple *ortho* substituents. For example, the synthesis of aryl (eq 3) and heteroaryl (eq 4) systems with tetra-*ortho*-substituted biaryl bonds has been reported.[4]



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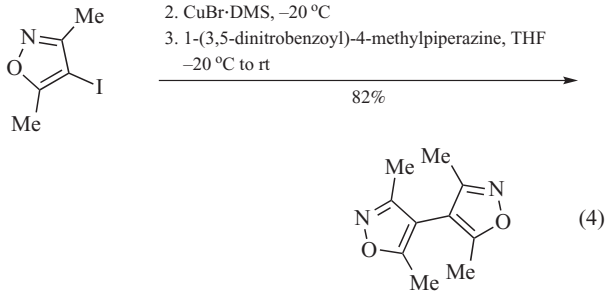
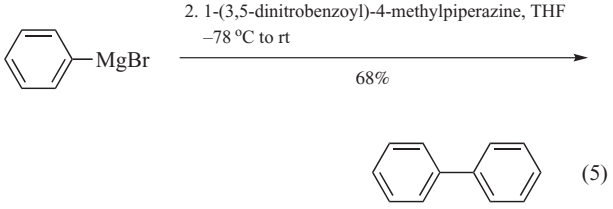


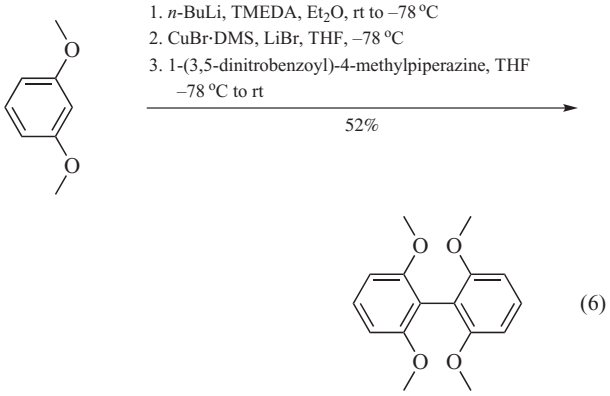
(4)

The use of 1-(3,5-dinitrobenzoyl)-4-methylpiperazine as the oxidant was crucial to the success of a reaction that used the aryl organocuprate derived from phenyl magnesium bromide (eq 5); when *meta*-dinitrobenzene was used, it proved difficult to obtain the pure product free of oxidant-derived by-products and other oxidants such as $FeCl_3$, $[Fe(acac)_3]$, $CuCl_2$, $LiCuCl_3$, $CrCl_2$, $LiNO_3$, $CeSO_4$, and DDQ gave unsatisfactory yields.[4]



(5)

Aryl lithium reagents formed by directed lithiation reactions have also been found to undergo transmetalation with CuBr·DMS to form aryl organocuprates that can be efficiently oxidized using 1-(3,5-dinitrobenzoyl)-4-methylpiperazine to yield *ortho*-substituted biaryls.[5] A range of directing groups proved effective for this process (including methoxy groups, alkoxy ethers, sulfonamides, carboxylates, and heterocycles). The coupling protocol allowed for an efficient synthesis of several biaryl bonds, including those in sterically hindered environments. For example, tetra-*ortho*-substituted biaryls could be accessed from substrates with a methoxy directing group (eq 6) and a carboxylate directing group (eq 7, TMP = 2,2,6,6-tetramethylpiperidine). It also proved possible to use an enantiopure valinol-derived oxazoline directing group to affect diastereoselective biaryl bond formation (eq 8); a single diastereoisomer was formed, albeit in a moderate yield.[5]



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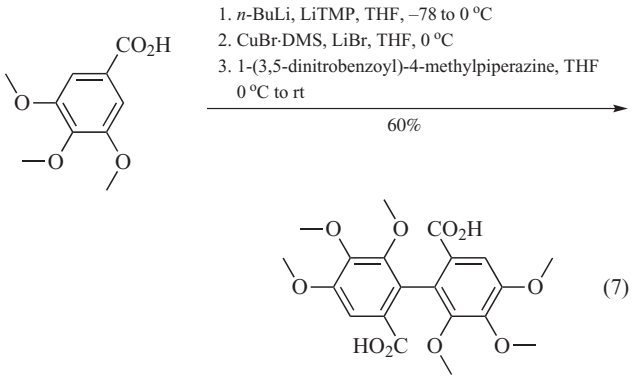

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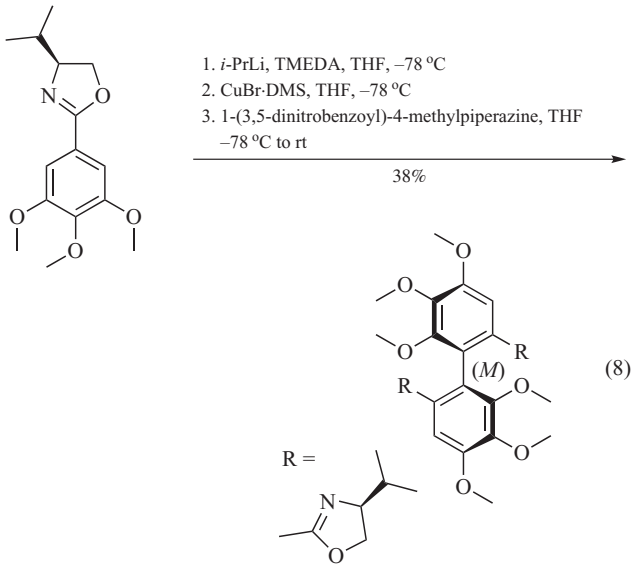
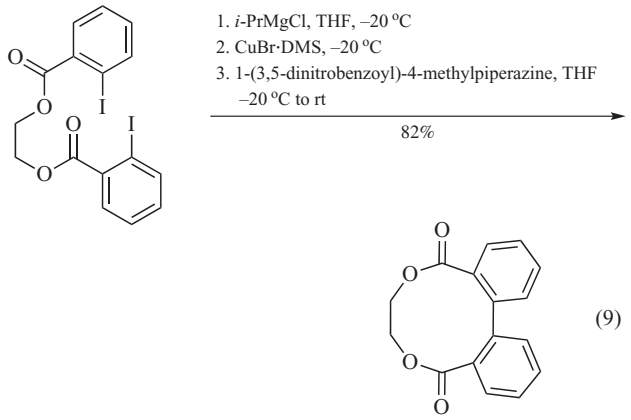


(8)

1-(3,5-Dinitrobenzoyl)-4-methylpiperazine has also been used to oxidize intramolecular aryl organocuprates resulting in concomitant biaryl bond and medium ring formation. For example, a 10-membered biaryl-containing ring system was prepared in a good yield from the corresponding diiodide (eq 9)[4] or dibromide (eq 10).[6] Notably, these organocuprate oxidation reactions did not require the use of high-dilution conditions.



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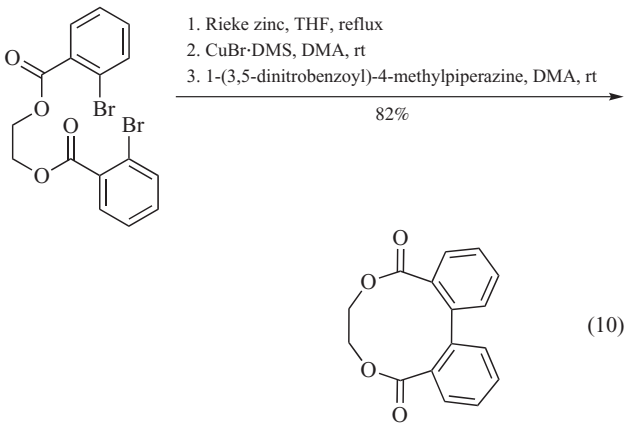
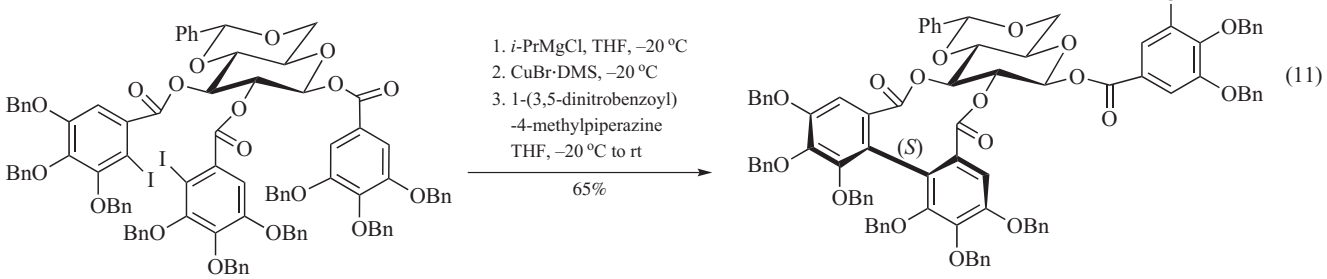


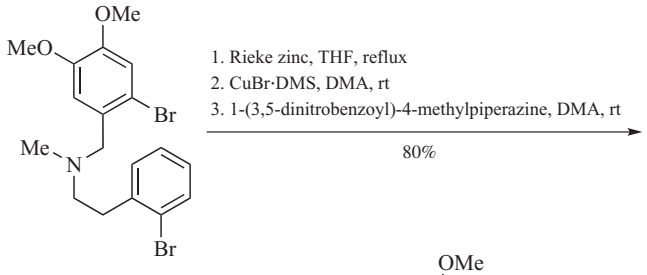
(10)

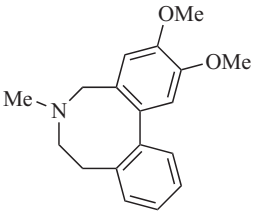
This approach has also been applied in the total synthesis of natural products. For example, the medium ring core of the ellagitannin natural product sanguiin H-5 was constructed using an organocuprate oxidative biaryl bond-forming reaction employing 1-(3,5-dinitrobenzoyl)-4-methylpiperazine (eq 11).[3,7] The reaction proceeded with complete diastereoselectivity for the desired (*S*)-atropisomer; high-dilution reaction conditions were not required and no dimer side products were observed.[3,7]



(11)

An intramolecular organocuprate oxidative reaction employing the same oxidant has also been used to generate the biaryl-containing medium ring core of the Amaryllidaceae alkaloid buflavine (eq 12).[6] This represented the first synthesis of this natural product where medium ring *and* biaryl formation was carried out in one step.

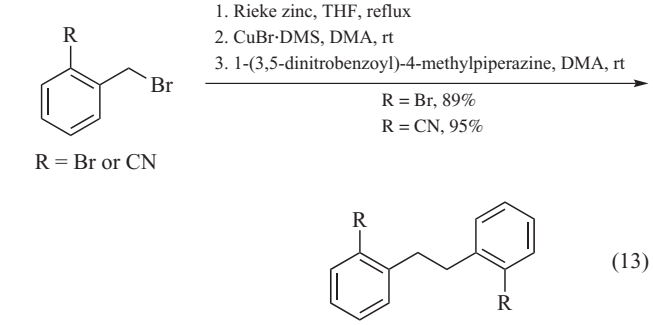




(12)

buflavine

Oxidation of Benzylic Organocuprates. The intermolecular homocoupling of benzylic organocuprates generated from benzyl bromides by a sequence of bromide–zinc exchange followed by transmetalation with CuBr·DMS has been reported (eq 13).[6] 1-(Chloromethyl)-4-methoxybenzene was also successfully coupled under these conditions (eq 14).



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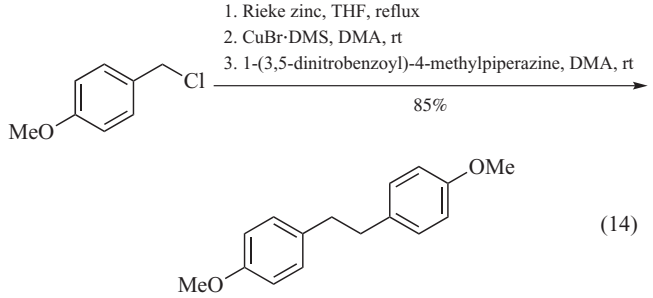
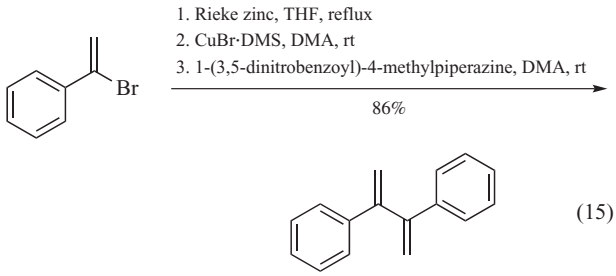


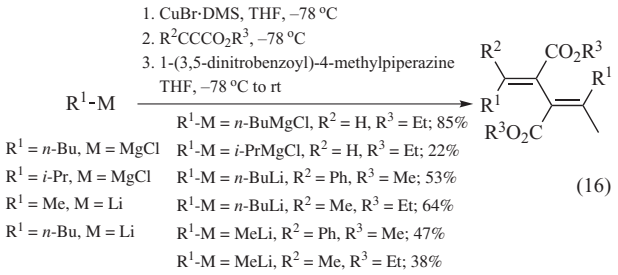
(14)

Oxidation of Alkenyl Organocuprates. The intermolecular coupling of the alkenyl organocuprate generated from α-bromostyrene (by a sequence of bromide–zinc exchange followed by transmetalation with CuBr·DMS) has been reported, using 1-(3,5-dinitrobenzoyl)-4-methylpiperazine as the oxidant (eq 15).[6]



(15)

Recently, a novel 'one-pot' tandem carbocupration/organocupration oxidation protocol has been developed that involves the in situ formation of an ester-substituted alkenyl cuprate from a terminal alkyne followed by oxidative coupling to furnish highly substituted symmetrical 1,3-dienes (eq 16).[8] The use of bromine in the place of 1-(3,5-dinitrobenzoyl)-4-methylpiperazine as the oxidant was examined, but a complex mixture of inseparable products resulted and there was no evidence for the formation of the desired product.



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