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Organocatalytic Domino Reaction of Electron-Deficient 2,4-Dienes with 2-Halo-1,3-Dicarbonyl Compounds: A Highly Regio- and Stereoselective Approach to Functionalized Five-Membered Carbocycles

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Abstract: An unexpected domino reaction of electron-deficient 2,4-dienes with 2-halo-1,3-dicarbonyl compounds, employing the readily available *N*-(4-trifluoromethylbenzyl)cinchonium bromide as the phase-transfer catalyst, provides an access to functionalized cyclopentenes and fulvene derivatives with excellent regio-, chemo- and stereoselectivities. A plausible mechanism for this unprecedented domino reaction is given.

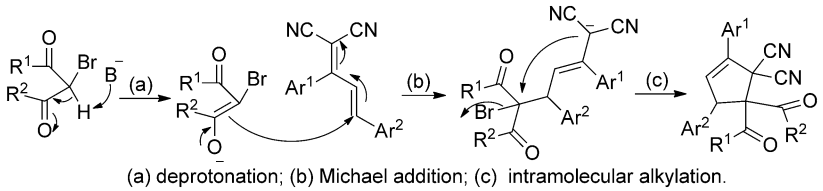
Keywords: cyclopentenes; 1,3-dicarbonyl compounds; domino reactions; fulvenes; organocatalysis

The five-membered carbocycles are constituents of a diverse assortment of natural products and biologically active agents,[1–3] and they are also valuable as synthetic building blocks to access drugs and agrichemical targets. Consequently new and efficient methods for the preparation of this important five-membered carbocyclic ring system are of contemporary interest. Despite the great success achieved for the formation of five-membered carbocycles, such as intramolecular Michael-type conjugate addition,[4,5] rearrangement,[6,7] intramolecular Morita–Baylis–Hillman reaction,[8] intramolecular ring-closing metathesis reaction,[9] intramolecular Wittig reaction,[10–12] and Nazarov cyclizations,[13] the construction of highly functionalized five-membered carbocycles remains challenging. Reactions that maximize molecular complexity with a minimum of operations and generate new C–C bonds are not only noteworthy but are also fundamental for the construction of five-membered rings. Domino reactions have been served as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials with minimized waste production.[14]

Herein, we report an efficient, mild, and convenient method for the preparation of fully substituted five-membered carbocycles *via* a novel domino reaction of electron-deficient 2,4-dienes with 2-halo-1,3-dicarbonyl compounds, by employing the readily available, low cost *N*-(4-trifluoromethylbenzyl)cinchonium bromide as phase-transfer catalyst under mild reaction conditions.

Recently, we have demonstrated that 1,3-dicarbonyl compounds and 2-halo-1,3-dicarbonyl compounds are readily available and attractive precursors for the construction of *O*-heterocycles *via* domino reactions.[15] In addition, α,α-dicyanoalkenes which are electron-deficient alkenes and inherently behave as electrophiles, have been employed as multifunctional synthons in the construction of complex molecules.[16,17] We envisioned that multifunctionalized cyclopentenes could be obtained by the domino reaction of 2-halo-1,3-dicarbonyl compounds with electron-deficient 2,4-dienes which were prepared from chalcone and malononitrile, as outlined in Scheme 1.

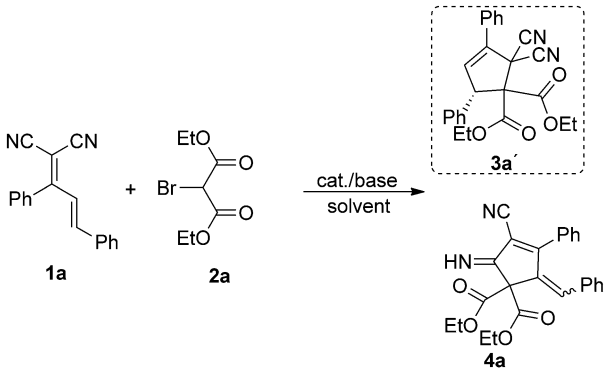
To explore the domino reaction, electron-deficient 2,4-diene (**1a**) and diethyl α-bromomalonate (**2a**) were first chosen for the initial screening. The model reaction was carried out in the presence of K_2CO_3 in dichloromethane (DCM) at room temperature for 24 h (entry 1, Table 1). Surprisingly, the result was not the one we expected but the unexpected multifunctionalized cyclopentene (**4a**) with three conjugated double bonds was obtained while the stereoselectivity is very poor ($Z/E = 50:50$, entry 1, Table 1). Then a series of organic solvents and bases was screened



Scheme 1. Potential strategies for the cyclization of 2-halo-1,3-dicarbonyl compounds with electron-deficient 2-(1,3-diphenylallylidene)malononitrile.

for this unexpected domino reaction. As shown in Table 1, only cyclopentene (**4a**) was obtained under different reaction conditions. In the presence of 100 mol% of a base, such as K_2CO_3 or DBU, **1a** was completely consumed within 24 h at room temperature providing **4a** in high yield, while the stereoselectivity is very poor (entries 1 and 2, Table 1). To our delight, the stereoselectivity was dramatically increased in the presence of 100 mol% K_2CO_3 and 20 mol% *N*-benzylcinchonium bromide **I** as chiral phase-transfer catalyst ($E/Z = 71:29$, entry 4, Table 1). When the base loadings were reduced to 50 mol%, the domino reaction provided **4a** in 79% yield with a high *E*-stereoselectivity ($E/Z = 93:7$, entry 5, Table 1). Other chiral phase-transfer catalysts derived from *Cinchona* alkaloids were then evaluated (Figure 1). We found that the introduction of an *N*-2′,3′,4′-trifluorobenzyl moiety such as in **II** instead of a *N*-benzyl group improves the catalytic activity and a good yield was obtained, while the stereoselectivity was decreased (entry 7, Table 1). The stereoselectivity was dramatically decreased when the bulkier β-naphthyl moiety was introduced to the chiral phase-transfer catalyst, such as **III** (entry 8, Table 1). *N*-(4-Trifluoromethylbenzyl)cinchonium bromide **IV** exhibited an excellent catalytic activity in the domino reaction and both excellent stereoselectivity and good yield were obtained ($E/Z = 96:4$, 76% yield, entry 9, Table 1). But the pseudoenantiomeric catalyst of **V**, *N*-(4-trifluoromethylbenzyl)cinchonidinium bromide, could give **4a** in poor stereoselectivity ($E/Z = 57:43$, entry 10, Table 1) under the same reaction conditions. Moreover, the hydroxy group also had an influence on the yield and stereoselectivity, as shown in entry 11. Chiral phase-transfer catalyst **VI**, which includes the *O*-allyl moiety, was found to be a less effective catalyst in the reaction and the stereoselectivity was decreased with poor yield ($E/Z = 91:9$, 40% yield, entry 11, Table 1). Subsequently, we investigated the effects of commonly used solvents and reaction temperature. Non-polar solvents, such as toluene and CH_2Cl_2, significantly increased the *E*-stereoselectivity (entries 9 and 12, Table 1) while the polar solvents, such as acetonitrile and acetone, decreased the *E*-stereoselectivity (entries 13 and 14, Table 1). In the hope of enhancing the *E*-stereoselectivity, the reaction was carried out in DCM at 15 °C using **IV** as the catalyst, the stereoselectivity was dramatically increased and only the *E*-isomer was obtained (entry 15, Table 1). Hence, running the domino reaction in DCM at 15 °C with 20 mol% **IV** as the chiral phase-transfer catalyst and 50 mol% K_2CO_3 appeared to be the optimal reaction conditions.

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst/Base	E/Z[b]	Yield [%][c]
1	DCM	–/K_2CO_3	50:50	98
2	DCM	–/DBU	50:50	98
3	DCM	–/DABCO	50:50	43
4	DCM	**I**/K_2CO_3	71:29	96
5[d]	DCM	**I**/K_2CO_3	93:7	79
6[e]	DCM	**I**/K_2CO_3	91:9	43
7[d]	DCM	**II**/K_2CO_3	83:17	81
8[d]	DCM	**III**/K_2CO_3	69:31	62
9[d]	DCM	**IV**/K_2CO_3	96:4	76
10[d]	DCM	**V**/K_2CO_3	57:43	34
11[d]	DCM	**VI**/K_2CO_3	91:9	40
12[d]	toluene	**IV**/K_2CO_3	96:4	60
13[d]	acetone	**IV**/K_2CO_3	87:13	77
14[d]	CH_3CN	**IV**/K_2CO_3	77:23	70
15[d,f]	DCM	**IV**/K_2CO_3	only *E*	74
16	DCM	**IV**	–	–

[a] Unless otherwise noted, reactions performed with 0.1 mmol of **1a**, 0.12 mmol of **2a**, 100 mol% base in solvent (1.0 mL) at room temperature for 24 h.
[b] Determined by ^{1}H NMR.
[c] Isolated yields.
[d] 50 mol% K_2CO_3 were added.
[e] 20 mol% K_2CO_3 were added.
[f] At 15 °C, 48 h.

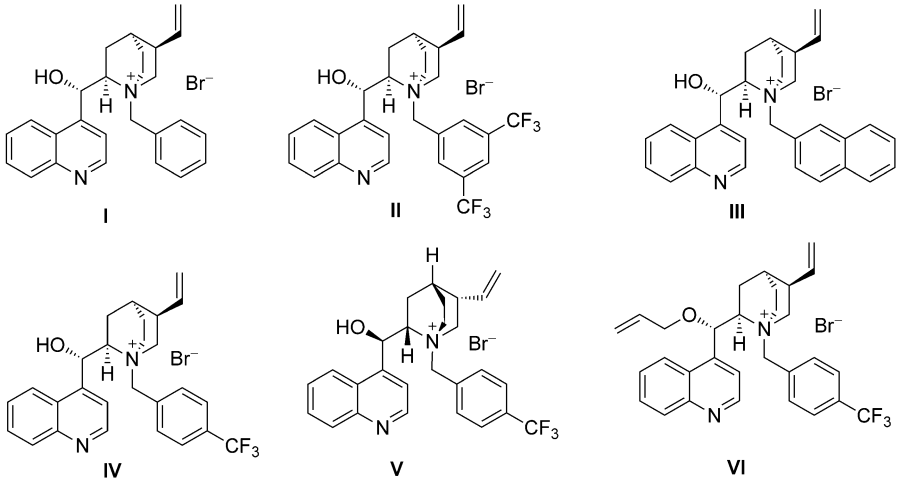
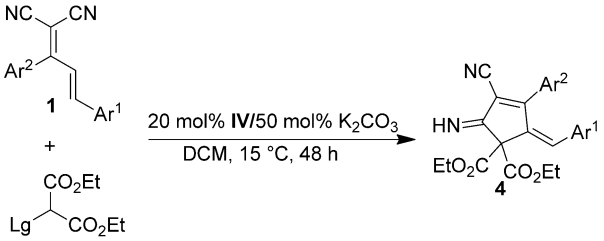


Figure 1. Chiral phase-transfer catalysts.

With the optimized reaction conditions in hand, we explored the scope of the unexpected domino reaction by using various electron-deficient 2,4-dienes **1** and the corresponding results are summarized in Table 2. Several points are noteworthy: (i) The scope of this unexpected domino reaction proved to be quite broad with respect to 2,4-dienes **1** and the novel transformations were highly stereoselective, simultaneously giving the highly substituted cyclopentenes with up to three conjugated double bonds. Interestingly, only *E*-isomers were detected for all the reactions. (ii) It appeared that substituents' electronics had a minimal impact on the efficiency of the domino reaction. Good yields were obtained in the domino reaction of **2a** with electron-withdrawing substituent on the aryl ring of 2,4-dienes **1** (entries 2–8, 11–13, Table 2). On the contrary, an electron-donating substituent on the aryl ring of 2,4-dienes **1** tended to decrease the yields (entries 9, 10, 14, 15, Table 2). (iii) The aromatic ring of 2,4-dienes **1** with electron-withdrawing substituents on the *ortho*, *meta* or *para* positions afford cyclopentenes with slightly inferior yields (entries 5–7, 11–13). (iv) On replacement of diethyl α-bromomalonate **2a** by other 2-halo-1,3-dicarbonyl compounds, such as diethyl α-chloromalonate **2b**, only the *E*-isomer with good yield was also obtained.

Interestingly, under similar conditions to the aforementioned ones, for ethyl 2-bromoacetoacetate **2c** which containa a CH_3CO group, unexpected products – fulvene derivatives **5** with good yields – were isolated (Table 3). Apparently the unexpected domino reaction took place to afford products **4**, and then a further retro-Claisen reaction occurred to generate the observed fulvene derivatives. Fulvenes and their derivatives have attracted much attention due to their unique properties in the fields of materials science, organometallics and medicinal chemistry since their discovery by Thiele in 1900.[18,19] However, they are traditionally made by the condensation of cyclopentadienes with a carbonyl compound, and this method is typically limited by the availability of the cyclopenta-

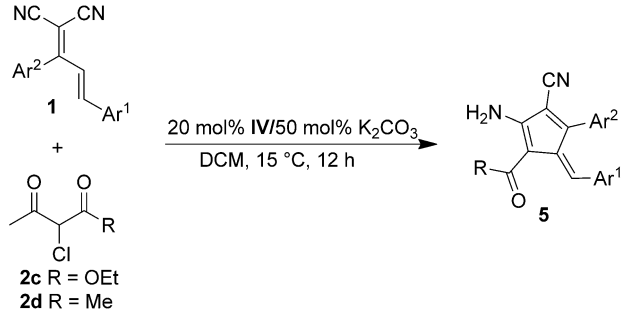
Table 2. Optimization of the reaction conditions.[a]



Entry	Ar^1	Ar^2	**1**	**2**	**4**	Yield [%][b]
1	Ph	Ph	**1a**	**2a**	**4a**	74
2	*p*-FC_6H_4	Ph	**1b**	**2a**	**4b**	80
3	*p*-BrC_6H_4	Ph	**1c**	**2a**	**4c**	77
4	*o*-BrC_6H_4	Ph	**1d**	**2a**	**4d**	73
5	*p*-ClC_6H_4	Ph	**1e**	**2a**	**4e**	78
6	*o*-ClC_6H_4	Ph	**1f**	**2a**	**4f**	77
7	*m*-ClC_6H_4	Ph	**1g**	**2a**	**4g**	73
8	2,5-$(Cl)_2C_6H_3$	Ph	**1h**	**2a**	**4h**	75
9	*p*-MeC_6H_4	Ph	**1i**	**2a**	**4i**	67
10	*p*-$MeOC_6H_4$	Ph	**1j**	**2a**	**4j**	60
11	Ph	*p*-ClC_6H_4	**1k**	**2a**	**4k**	77
12	Ph	*o*-ClC_6H_4	**1l**	**2a**	**4l**	72
13	Ph	*m*-ClC_6H_4	**1m**	**2a**	**4m**	76
14	Ph	*p*-MeC_6H_4	**1n**	**2a**	**4n**	68
15	Ph	*p*-$MeOC_6H_4$	**1o**	**2a**	**4o**	62
16	Ph	Ph	**1a**	**2b**	**4a**	71

[a] Unless otherwise noted, reactions performed with 0.1 mmol of **1**, 0.12 mmol of **2**, 50 mol% base and 20 mol% **IV** in DCM (1.0 mL) at 15 °C for 48 h.
[b] Isolated yields.

Table 3. Synthesis of the substituted fulvene derivatives **5**.[a]



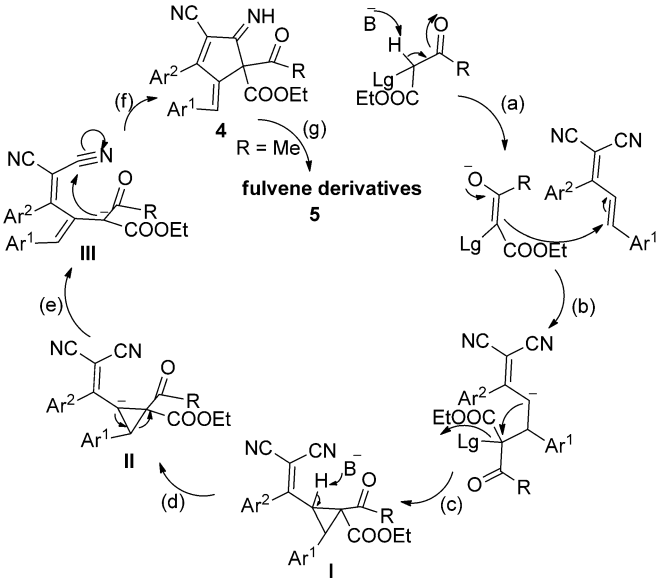
Entry	Ar^1	Ar^2	1	2	5	Yield[b] [%]
1	Ph	Ph	**1a**	**2c**	**5a**	66
2	*p*-FC_6H_4	Ph	**1b**	**2c**	**5b**	87
3	*p*-BrC_6H_4	Ph	**1c**	**2c**	**5c**	76
4	*o*-BrC_6H_4	Ph	**1d**	**2c**	**5d**	77
5	*p*-ClC_6H_4	Ph	**1e**	**2c**	**5e**	70
6	*o*-ClC_6H_4	Ph	**1f**	**2c**	**5f**	61
7	*m*-ClC_6H_4	Ph	**1g**	**2c**	**5g**	62
8	2,5-$(Cl)_2C_6H_3$	Ph	**1h**	**2c**	**5h**	73
9	*p*-MeC_6H_4	Ph	**1i**	**2c**	**5i**	64
10	Ph	*p*-ClC_6H_4	**1k**	**2c**	**5j**	83
11	Ph	*o*-ClC_6H_4	**1l**	**2c**	**5k**	62
12	Ph	*m*-ClC_6H_4	**1m**	**2c**	**5l**	67
13	Ph	*p*-BrC_6H_4	**1p**	**2c**	**5m**	87
14	Ph	*p*-MeC_6H_4	**1n**	**2c**	**5n**	77
15	Ph	*p*-$MeOC_6H_4$	**1o**	**2c**	**5o**	66
16	Ph	Ph	**1a**	**2d**	**5p**	62

[a] Unless otherwise noted, reactions performed with 0.1 mmol of **1**, 0.12 mmol of **2**, 50 mol% base and 20 mol% **IV** in DCM (1.0 mL) at 15 °C for 12 h.
[b] Isolated yields.

dienes prepared from multistep procedures, in which regioselectivity and functional group tolerance are often major difficulties. As such, we turned our attention to the synthesis of fulvene derivatives **5** from electron-deficient 2,4-dienes **1**. To assess the impact of the structural and functional motifs on the reaction, we tested a range of electron-deficient 2,4-dienes **1**, and the corresponding results are summarized in Table 3. The reaction scope proved to be broad with respect to electron-deficient 2,4-dienes **1**. These novel transformations were highly stereoselective and only the *E*-isomers were detected for all the reactions. It appeared that substituents' electronics had a minimal impact on efficiencies of the domino reaction. Electron-deficient 2,4-dienes **1** with substituents on the *meta* or *ortho* positions as well as electron-deficient 2,4-dienes **1** with electron-denoting substituents on the *para* positions afford fulvene derivatives **5** with slightly inferior yields (entries 6, 7, 9, 11, 12 and 15, Table 3). The replacement of ethyl 2-bromoacetoacetate **2c** by 3-chloropentane-2,4-dione **2d**, fulvene derivative **5p** was also obtained in moderate yield (entry 16, Table 3).

The regio- and stereochemistry of the substituted cyclopentenes and fulvene derivatives were confirmed by the X-ray diffraction analysis of **4f** and **5h** (Figure 2).

On the basis of the experimental observations, a possible mechanism was proposed to explain the unexpected one-pot tandem reaction. As shown in Scheme 2, the Michael reaction proceeded smoothly between electron-deficient 2,4-dienes and 2-halo-1,3-dicarbonyl compounds under the base conditions, fol-



(a) deprotonation; (b) Michael addition; (c) iIntramolecular alkylation; (d) deprotonation; (e) ring-opening; (f) intramolecular nucleophilic addition; (g) retro-Claisen reaction.

Scheme 2. Plausible reaction mechanism.

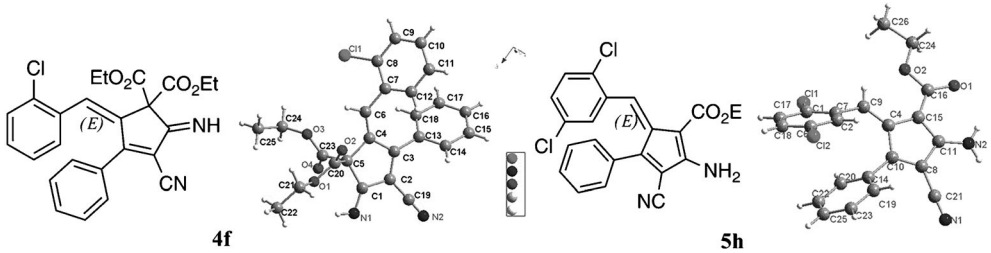


Figure 2. X-ray diffraction analysis of **4f** and **5h**.

lowed by alkylation to afford intermediate cyclopropane derivatives **I**. Because the γ-C–H of electron-deficient dicyanoalkenes was easily deprotonated under base conditions,[16,17] carbanion **II** was formed under base conditions, and subsequent ring-opening helped by a lone pair of **II** afforded intermediate **III**. Then, the intramolecular nucleophilic addition of the carbanion group of **III** on the cyano moiety took place to form products **4**. A further retro-Claisen condensation occurred to generate the observed fulvene derivatives **5** when the group R is methyl.

In summary, we have successfully demonstrated a novel domino Michael/alkylation/vinylcyclopropane rearrangement of electron-deficient 2,4-dienes **1** to 2-halo-1,3-dicarbonyl compounds **2** for the synthesis of multifunctional cyclopentenes with excellent regio-, chemo-, and stereoselectivity, by employing readily available, low cost *N*-(4-trifluoromethylbenzyl)cinchonium bromide **IV** as the phase-transfer catalyst. Fully substituted fulvene derivatives were also obtained through a further retro-Claisen reaction. Notably, the reaction scope is quite substantial and only the *E*-isomers were detected. A plausible mechanism for this unprecedented domino reaction was given. Further investigations to expand the synthetic utilities of this protocol, such as synthesis of pharmaceutically intriguing compounds, are currently underway.

Experimental Section

Typical Experimental Procedure for the Domino Reaction of 2,4-Dienes 1 and 2-Halo-1,3-dicarbonyl Compounds 2 (entry 1, Table 2)

Catalyst **IV** (10.6 mg, 20 mol%) was added to the solution of 2,4-diene **1a** (26.0 mg, 10 mmol) and diethyl α-bromomalonate **2a** (30.0 mg, 0.12 mmol) in DCM (1.0 mL) at 15 °C. Then K_2CO_3 (7.0 mg, 0.05 mmol) was added. The mixture was stirred at 15 °C for 48 h. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give **4a**; yield: 30 mg (74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.39 (s, 1H), 7.61 (s, 1H),7.31 (s, 1H), 7.25–7.11 (m, 5H), 6.99 (d, J = 8.1 Hz, 1H), 6.89 (t, J = 7.7 Hz, 1H), 6.79–6.76 (m, 2H), 4.36 (q, J = 7.1 Hz, 4H), 1.34 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 166.5, 165.2, 135.7, 135.6, 135.1, 133.5, 131.1, 130.3, 129.8, 129.3, 129.2, 129.0, 128.7, 128.3, 128.1, 127.8, 127.2, 118.9, 112.9, 68.3, 63.4, 13.9. ESI-HR-MS: m/z = 437.1492, calcd. for [$C_{25}H_{22}N_2O_4$ + Na]: 437.1472.

Crystallographic Data for 4f

$C_{25}H_{21}ClN_2O_4$ (448.89). Monoclinic, space group $P21/c$, a = 11.5422(3) Å, b = 18.0929(4) Å, c = 11.1757(3) Å, V = 2304.09(10) Å^3, Z = 13, specimen 0.334 × 0.206 × 0.172 mm^3, T = 296(2) K, Siemens P4 diffractometer, absorption coefficient 0.199 mm^{-1}, reflections collected 20223, independent 5282 [R(int) = 0.0766], refinement by full-matrix least-squares on F^2, data/restraints/parameters 5282/0/294, goodness-of-fit on F^2 = 0.986, final R indices [I > 2 sigma(I)] $R1$ = 0.0550, $wR2$ = 0.1317, R indices (all data) $R1$ = 0.1464, $wR2$ = 0.1692, largest diff. peak and hole 0.247 and −0.201 Å^{-3}. CCDC 954456 contains the supplementary crystallographic data for the structure of **4f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: (internat.) (+44)-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Crystallographic Data for 5h

$C_{22}H_{16}Cl_2N_2O_2$ (411.27). Triclinic, space group P-1, a = 9.6224(5) Å, b = 10.3070(5) Å, c = 11.4274(5) Å, V = 1000.76(8) Å^3, Z = 4, specimen 0.263 × 0.216 × 0.132 mm^3, T = 296(2) K, Siemens P4 diffractometer, absorption coefficient none, reflections collected 15828, independent 4517 [R-(int) = 0.0235], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 4517/0/254, goodness-of-fit on F^2 = 1.078, final R indices [I > 2 sigma(I)] $R1$ = 0.0357, $wR2$ = 0.0907, R indices (all data) $R1$ = 0.0478, $wR2$ = 0.0478, largest diff. peak and hole 0.249 and −0.285 Å^{-3}. CCDC 954457 contains the supplementary crystallographic data for the structure of **5h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: (internat.) (+44)-1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

Experimental procedures, characterization data and model of possible transition states of the reaction are available in the Supporting Information in detail.

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