Tetrahedron 67 (2011) 7586–7592

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Carbon–carbon bond-forming reactions of α-carbonyl carbocations: exploration of a reversed-polarity equivalent of enolate chemistry

Ping-Shan Lai, Joshua A. Dubland, Mohammed G. Sarwar, Michael G. Chudzinski, Mark S. Taylor *

Department of Chemistry, University of Toronto, 80 St. George St., Toronto, ON M5S 3H6, Canada

ARTICLE INFO

Article history:
Received 17 May 2011
Received in revised form 18 July 2011
Accepted 20 July 2011
Available online 27 July 2011

Keywords:
Carbocations
Friedel–Crafts reaction
Allylation
Lactams
Umpolung reactivity

ABSTRACT

Carbon–carbon bond-forming reactions of putative α-carbonyl carbocation intermediates generated by Lewis acid- or silver-promoted ionizations of toluenesulfonate or halide leaving groups are described. This under-exploited mode of reactivity represents an 'umpolung' of conventional enolate chemistry, and enables C–C bond construction in both intra- and intermolecular contexts. Attempts to develop diastereoselective variants of this process using chiral ester and oxazolidinone-based auxiliaries are discussed.

1. Introduction

Formation of carbon–carbon bonds α to the carbonyl group is dominated by the chemistry of enolates and their derivatives. Despite the diverse reactivity of this class of nucleophiles—including aldol and Mannich-type additions, S_N2 and S_N1 reactions with alkylating agents, and transition metal-catalyzed arylations—the development of reversed-polarity ('umpolung') equivalents of enolate-based C–C bond construction is of considerable interest. Several such modes of reactivity have been devised and exploited in synthesis:[1] among the most widely applied are S_N2-type reactions of carbon nucleophiles with epoxides, α-halo ketones,[2] and related reagents, additions to vinyl nitro or nitroso-type electrophiles,[3] and oxidative couplings of enolates.[4]

The addition of carbon-based nucleophiles to α-carbonyl carbocations represents a potentially useful, but poorly studied, reversed-polarity equivalent of the enolate reactivity pattern. Although the inductive effect of the carbonyl group might be expected to destabilize carbocations of this type, fundamental studies by the groups of Creary and Charpentier-Morize have demonstrated that they are in fact viable reactive intermediates.[5] Both anchimeric (*n*-participation) and resonance (π-delocalization) effects have been invoked to rationalize the unexpected stability of α-carbonyl carbocations.[6] In comparison to the rather extensive physical–organic chemistry studies of this type, there have been relatively few attempts to exploit such intermediates in synthetic methodology. Carbon–carbon bond-forming reactions in which leaving groups adjacent to carbonyl groups are displaced by electron-rich alkenes or arenes are limited in scope and variable in yield;[7] in certain instances, stereochemical outcomes consistent with S_N2-type mechanisms have been observed.[7f] (It is important to draw a distinction between α-carbonyl carbocations and 2-oxyallylic carbocations: the latter, which presumably benefit from a higher degree of stabilization, show a rich chemistry, particularly in the context of cycloaddition reactions.[8]) In a recent development, Johnson and Smith described Lewis acid-promoted S_N1 reactions of α-aryl-α-ketophosphonates with electron-rich arenes, as well as other carbon- and heteroatom-centered nucleophiles.[9] Here, we describe the development of mild, general reaction conditions enabling efficient nucleophilic substitution α to carboxyl groups by electron-rich π nucleophiles (alkenes and arenes). Our results differ from those of Johnson and co-worker by: (1) the use of substrates derived from amides and esters (rather than ketones) as substrates; (2) the development of intramolecular variants, enabling the preparation of useful classes of heterocycles; (3) the mode of generation of the putative α-carbonyl cation intermediates. These highly electrophilic intermediates enable the use of relatively unreactive nucleophiles in both intra- and intermolecular contexts, and present interesting opportunities for stereocontrol: our efforts to carry out diastereoselective additions to chiral α-carbonyl carbocations are described.

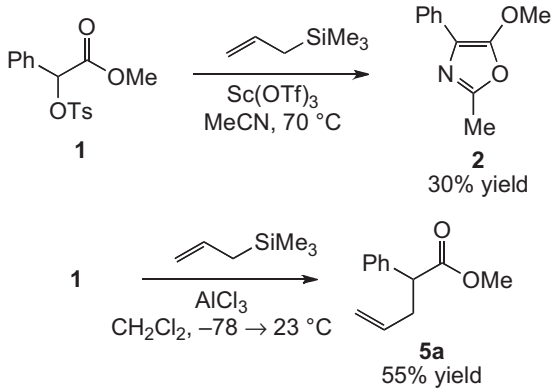
* Corresponding author. E-mail address: mtaylor@chem.utoronto.ca (M.S. Taylor).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.07.065

2. Results and discussion

2.1. Optimization of conditions for intermolecular nucleophilic displacements α to carbonyl groups by arenes and alkenes

Our initial efforts were centered on reactions of sulfonate or carboxylate substrates derived from readily available α-hydroxycarbonyl compounds: a range of nucleophiles, leaving groups, Brønsted and Lewis acids were evaluated. Reaction with allyltrimethylsilane with tosylate **1** in the presence of scandium(III) trifluoromethanesulfonate (triflate) in acetonitrile solvent unexpectedly provided oxazole **2**, presumably through a Ritter-type reaction (Scheme 1). After optimization, this proved to be a general method for the preparation of oxazoles from α-oxo tosylates; the results are described in detail in a previous publication.[10] The product of carbon–carbon bond formation (**5a**) was obtained in modest yield by reaction of **1** with allyltrimethylsilane using aluminum(III) chloride as a promoter (Scheme 1). Experiments with enantioenriched **1** resulted in the formation of racemic **5a**, consistent with a reaction mechanism involving an α-carbonyl carbocation intermediate. However, it proved difficult to improve or extend this result: the yield was highly solvent- and Lewis acid-dependent,[11] and employing other nucleophiles (electron-rich alkenes or arenes) or electrophiles (for example, replacing the ester group in **1** with an amide group) did not afford useful yields of the desired products of nucleophilic displacement.

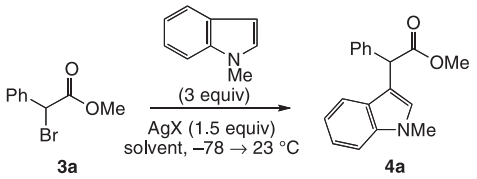


Scheme 1. Lewis acid-promoted substitution reactions of tosylate **1**.

We turned our attention to silver(I)-promoted reactions of α-bromoester **3a**, in the hopes of developing reaction conditions that would be of more general synthetic utility. Variation of the silver salt AgX and the solvent had a significant effect on the yield of reactions of **3a** with 1-methylindole (Table 1). Previous studies using Ag(I) salts to generate α-carbonyl carbocations have employed non-coordinating counterions, such as BF_4^- or SbF_6^-; in our hands, counterions of intermediate coordinating ability (trifluoroacetate and triflate) provided the highest yields.

Under the optimized reaction conditions, a range of arenes engaged in Friedel–Crafts reactions with α-bromoester **3a** (Table 2, entries 1–6). Efficient reaction with unsubstituted benzene was observed, and did not require the use of the latter as reaction solvent. The method is tolerant of replacement of the ester group with an amide (entry 7), and of substitution of the aromatic ring in **3a** (entry 8); however, substrates **3** lacking the carbocation-stabilizing aryl group Ar did not participate in Friedel–Crafts reactions under these conditions. In addition to arenes, allyl- and methallyltrimethylsilane underwent Ag(I)-promoted carbon–carbon bond-forming reactions with **3a**, **3b**, and **3d** (Scheme 2). In the absence of added base, the reaction of **3a** with methallyltrimethylsilane

Table 1
Optimization of reaction conditions for the Ag(I)-promoted Friedel–Crafts reaction of **3a**



Entry	AgX	Solvent	Yield[a] (%)
1	AgOAc	CH_2Cl_2	0
2	Ag_2CO_3	CH_2Cl_2	0
3	AgOTs	CH_2Cl_2	30
4	$AgClO_4$	CH_2Cl_2	40
5	$AgSbF_6$	CH_2Cl_2	55
6	$AgPF_6$	CH_2Cl_2	70
7	$AgBF_4$	CH_2Cl_2	85
8	$AgOCOCF_3$	CH_2Cl_2	95
9	AgOTf	CH_2Cl_2	95
10	AgOTf	THF	70
11	AgOTf	Toluene	50
12	AgOTf	MeCN	70

[a] Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as a quantitative internal standard.

resulted in the formation of lactone **5e**. In the presence of 2,6-lutidine, methallylated product **5d** was obtained, consistent with the hypothesis that the triflic acid byproduct promoted the cyclization of **5d** to generate **5e**.

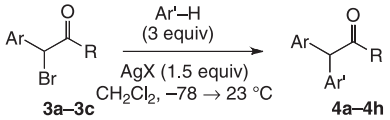
2.2. Synthesis of heterocycles by intramolecular Friedel–Crafts reactions of α-bromoesters and -amides

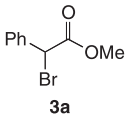
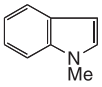
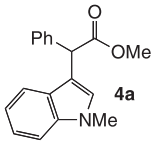
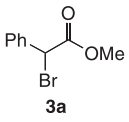
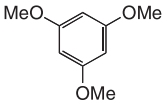
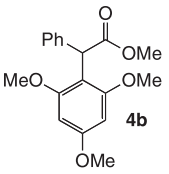
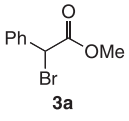
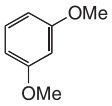
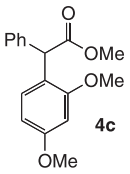
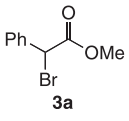
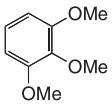
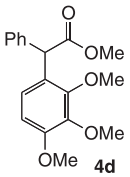
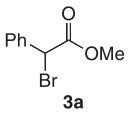
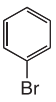
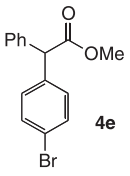
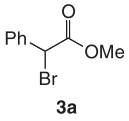
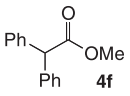
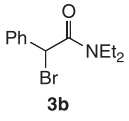
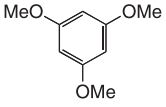
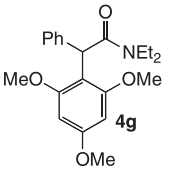
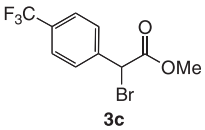
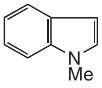
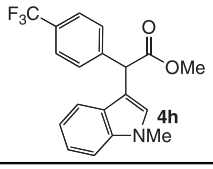
We pursued intramolecular variants of the reactions described above, with the goal of developing efficient syntheses of lactams and lactones by Friedel–Crafts cyclization reactions. The closest precedent for such transformations is work of the group of Levacher, who reported five examples of δ-lactam formation from α-acetoxy amides promoted by sulfuric acid (20–86% yield).[7f] Experiments with enantioenriched α-acetoxy amide substrates demonstrated that these reactions proceeded with inversion of stereochemistry, the extent of which depended on the substitution pattern of the nucleophilic aryl group. Under the Ag(I)-mediated conditions, γ- and δ-lactams with a range of substitution patterns (**7a**–**f**), as well as a γ-lactone (**7g**), were generated smoothly from the corresponding α-bromocarbonyl compounds (Table 3). The 3-aryl-oxindole and 4-aryltetrahydroisoquinoline ring systems obtained are core structures of a wide range of biologically active compounds.

2.3. Studies of diastereoselective substitution reactions of chiral α-carbonyl carbocations

The ability of chiral auxiliaries or catalysts to control the stereochemical outcome of enolate reactions has been crucial to the broad utility of these intermediates in complex target synthesis. In contrast, stereoselective additions to carbocations, whether catalyst- or auxiliary-controlled, represent a significant and largely unsolved problem for organic synthesis. The methods discussed above would appear to be ideal starting points for the development of diastereoselective carbon–carbon bond-forming reactions controlled by chiral ester or amide groups. We were intrigued by the prospect that cation–π or cation–*n* interactions, which have arguably been under-exploited as the basis for selectivity in organic reactions,[12] might be employed productively in this context. It is important to point out pioneering work by Heaney and co-workers,

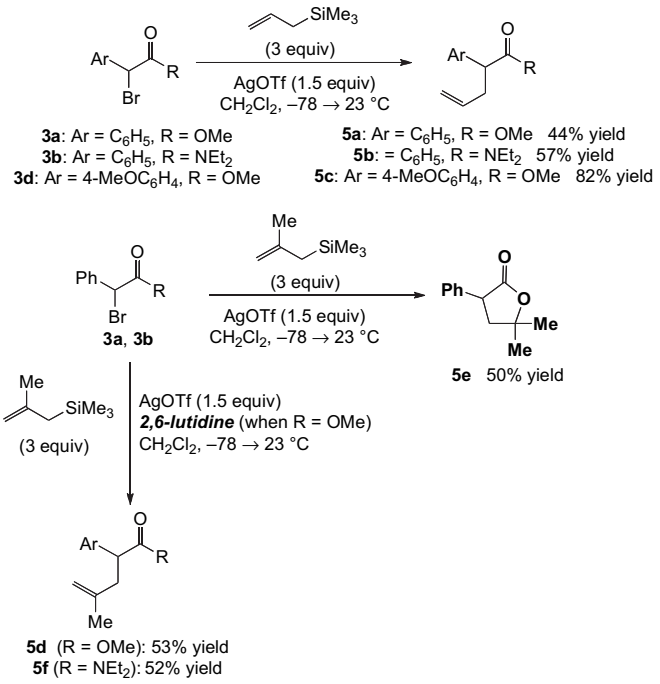
Table 2
Ag(I)-promoted Friedel–Crafts reactions of α-bromocarbonyl compounds



Entry	Substrate	Ar'–H	Product	Yield[a] (%)
1	 **3a**		 **4a**	92
2	 **3a**		 **4b**	83
3	 **3a**		 **4c**	80
4	 **3a**		 **4d**	73
6	 **3a**		 **4e**	84[b]
7	 **3a**		 **4f**	80[c]
8	 **3b**		 **4g**	78
9	 **3c**		 **4h**	83

[a] Isolated yield of pure product after column chromatography on silica gel. AgOTf was employed in all entries except 3 and 9, for which AgO_2CCF_3 was employed.
[b] Isolated as a 7:1 *para*/*ortho* isomer mixture.
[c] C_6H_6 (10 equiv) was employed.

who developed diastereoselective additions of indole and pyrrole nucleophiles to 2-indolylacetate-derived carbocations bearing the 9-phenylmenthyl chiral auxiliary.[13] It was not clear to us whether this process could be extended to more reactive carbocation intermediates that do not benefit from vinylogous iminium-type stabilization. In this regard, the recent results of Bach and co-workers constitute important precedent: they have demonstrated that conformational and stereoelectronic effects may be brought to



Scheme 2. Reactions of α-bromocarbonyl compounds with allylsilane reagents.

bear to achieve highly diastereoselective additions to benzylic carbocations bearing adjacent chirality centers.[14] Their studies indicate that stereoselectivity is possible in additions to highly electrophilic carbocation intermediates.

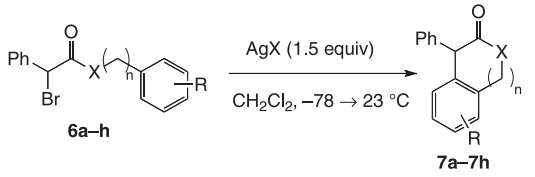
Preliminary computational investigations of benzylic carbocations bearing chiral ester (**8a**–**c**) and oxazolidinone (**8d**) auxiliaries were conducted. The calculated optimum geometries (gas phase, B3LYP/6-31+G(d)), depicted in Fig. 1, illustrate an interesting range of possibilities.[15] For cations **8a** and **8b**, which bear Whitesell-type[16] 2-arylcyclohexanol auxiliaries, the 2-aryl group does not appear to engage in cation–π contacts in the calculated structure, but nonetheless occupies a position that at least partially hinders approach to one of the two diastereotopic faces. On the other hand, a cation–π interaction is evident in the calculated geometry of phenylmenthol-based[17] cation **8c**. The computed structure of *N*-acyloxazolidinone-derived[18] carbocation **8d** is characterized by a cation–*n* interaction with the imide carbonyl group.

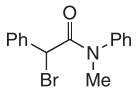
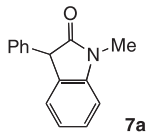
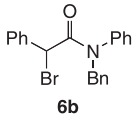
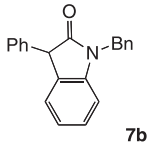
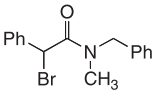
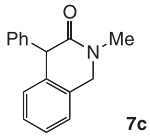
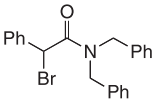
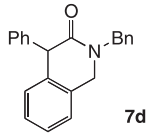
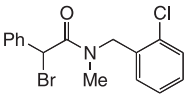
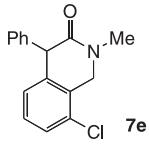
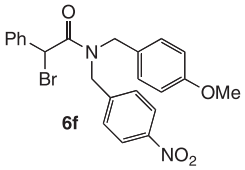
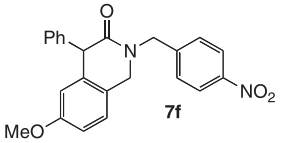
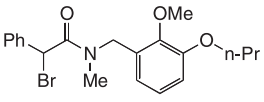
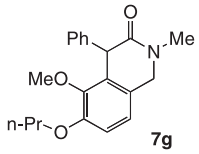
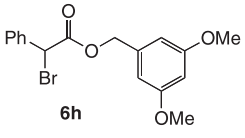
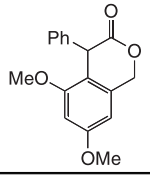
The synthesis of chiral α-bromoesters **9a**–**c** and α-bromoimide **9d** were then undertaken (Scheme 3). While the former were prepared in a straightforward fashion by carbodiimide-mediated couplings of alcohols with α-bromophenylacetic acid, the latter proved to be a more challenging target. Acylation of lithiated oxazolidinone with α-bromophenylacetyl chloride[19] resulted in an inseparable mixture of α-bromo- and α-chloroimide products, as judged by mass spectrometric (MS) analysis. Ultimately, **9d** was obtained in pure form by modest-yielding bromination of an imide-derived enolate.[20]

Silver(I)-promoted reactions of **9a**–**d** with *N*-methylindole under a range of reaction conditions provided the desired products of Friedel–Crafts alkylation, but with uniformly low levels of diastereoselectivity. Representative results are collected in Table 4. Variation of the counterion X and the reaction medium had little effect on the observed diastereomeric ratio. The addition of a second, chelating Lewis acid to reactions of **9d**—with the idea of using two-point binding to reduce conformational flexibility about the N–C bond—did not influence the diastereomeric ratio (1.4:1 and 1.3:1 dr were obtained: data not shown).

The possibility that intramolecular Friedel–Crafts reactions might offer improved prospects for achieving diastereoselectivity

Table 3
Friedel–Crafts cyclizations of α-bromoamides and esters



Entry	Substrate	Product	Yield[a] (%)
1	 **6a**	 **7a**	>99
2	 **6b**	 **7b**	>99
3	 **6c**	 **7c**	82
4	 **6d**	 **7d**	86
5	 **6e**	 **7e**	66
7	 **6f**	 **7f**	57
8	 **6g**	 **7g**	55
9	 **6h**	 **7h**	66

[a] Isolated yield of pure product after column chromatography on silica gel. AgO_2CCF_3 was employed for all entries except 5 ($AgBF_4$), 9, and 10 (AgOTf).

was investigated in the context of α-methylbenzyamine-derived amides **11a** and **11b**. As in the intermolecular cases, disappointing levels of diastereoselectivity were observed with a range of promoters AgX (Table 5). Diastereomerically pure **12b** was isolated and

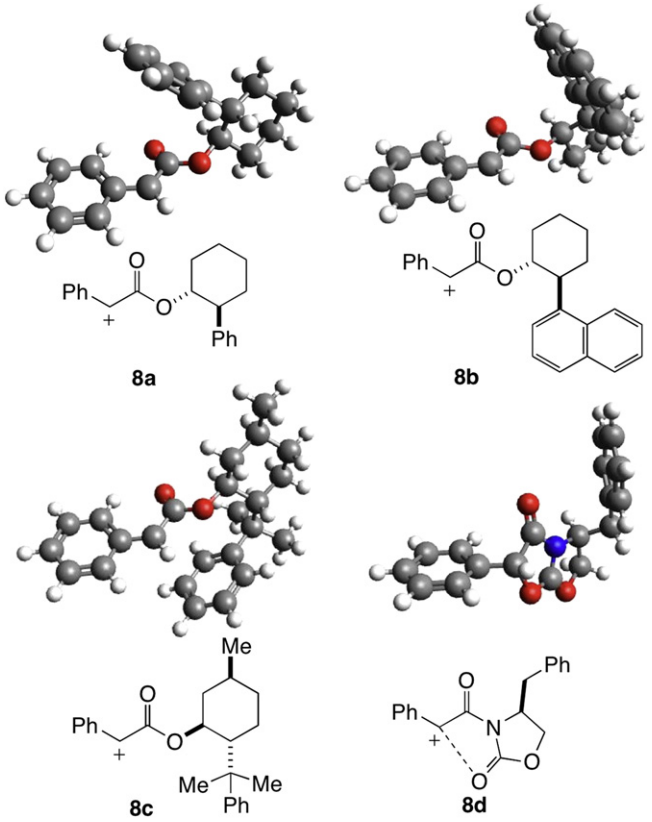
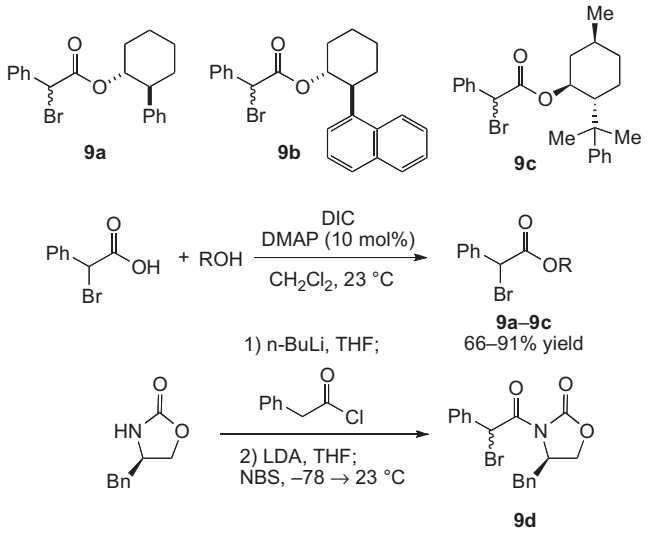


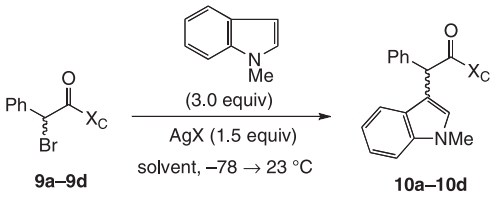
Fig. 1. Calculated (B3LYP/6-31+G(d)) gas-phase structures of chiral carbocations **8a**–**e**.



Scheme 3. Preparation of chiral auxiliary-derived α-bromocarbonyl compounds **9a**–**d**.

recovered unchanged after being resubmitted to the reaction conditions, suggesting that the mixtures obtained do not result from a thermodynamically controlled process in this case. Experiments employing different batches of **11a**–**b** varying in their diastereomeric ratio provided interesting results. Cyclization of **11a** furnished **12a** with the same diastereoselectivity regardless of the dr of starting material employed, consistent with the involvement of a carbocation intermediate. In contrast, the dr of **12b** was dependent on that of starting material **11a**, suggesting an S_N2-type process; this effect was observed with AgOTf but not with the less coordinating PF_6^- counterion. The higher nucleophilicity of the

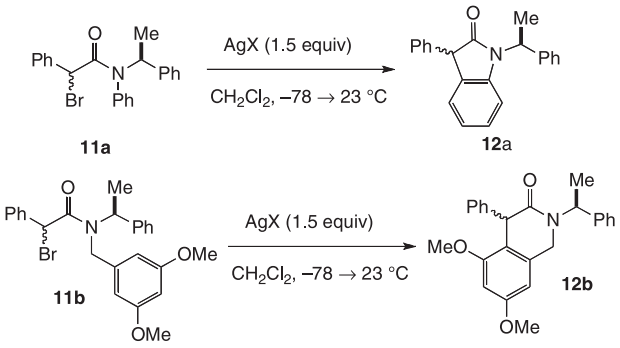
Table 4
Silver(I)-promoted Friedel–Crafts reactions of **9a**–**d** with *N*-methylindole



Entry	Substrate	AgX	Solvent	% Yield[a]	dr[b]
1	**9a**	AgOTf	CH_2Cl_2	70	2.3:1
2	**9a**	AgOTf	THF	95	1.8:1
3	**9a**	AgOTf	CH_3CN	80	1.7:1
4	**9a**	$AgPF_6$	CH_2Cl_2	90	1.8:1
5	**9a**	AgOTs[c]	DCE	95	2.1:1
6	**9b**	AgOTf	CH_2Cl_2	85	1.4:1
7	**9c**	AgOTf	CH_2Cl_2	75	1.4:1
8	**9d**	AgOTf	CH_2Cl_2	30	1.3:1

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as a quantitative internal standard.
[b] Diastereomeric ratio (dr) determined by ^{1}H NMR. The relative configuration of the major diastereomer was not determined.
[c] Reaction was carried out at 23→70 °C.

Table 5
Intramolecular Friedel–Crafts reactions of chiral amides **11a** and **11b**



Entry	Substrate	AgX	% Yield[a]	dr[b]
1	**11a** (1.5:1 dr)	$AgOCOCF_3$	>95	1.1:1
2	**11a** (3.2:1 dr)	$AgOCOCF_3$	>95	1.2:1
3	**11b** (2.4:1 dr)	$AgOCOCF_3$	50	1.1:1
4	**11b** (2.4:1 dr)	$AgClO_4$	65	2.4:1
5[c]	**11b** (2.4:1 dr)	$AgBF_4$	80	2.4:1
6	**11b** (2.4:1 dr)	$AgSbF_6$	85	2.2:1
7	**11b** (2.4:1 dr)	$AgPF_6$	88[d]	1.7:1
8	**11b** (1.2:1 dr)	$AgPF_6$	67	1.1:1
9	**11b** (2.4:1 dr)	AgOTf	92	2.4:1
10	**11b** (1.2:1 dr)	AgOTf	68	1.2:1

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as a quantitative internal standard.
[b] Diastereomeric ratio (dr) determined by ^{1}H NMR. The relative configuration of the major diastereomer was not determined.
[c] Reaction was carried out at −78→50 °C.
[d] Isolated yield (mixture of diastereomers) after column chromatography.

electron-rich arene nucleophile employed in this case may underlie the mechanistic differences between the reactions of **11a** and **11b**.

3. Conclusions

Silver(I)-promoted reactions of α-halocarbonyl compounds with arene and alkene nucleophiles represent a useful reversed-polarity equivalent of the carbon–carbon bond-forming reactions of enolates. The ability of unactivated arenes, such as benzene to function as nucleophiles in such transformations apparently reflects the highly electrophilic nature of the putative α-carbonyl

carbocation intermediates. Intramolecular reactions of this type provide a novel and efficient means of access to oxindole and dihydroisoquinolinone ring systems. Although calculations point toward interesting opportunities for attractive intramolecular contacts in derivatives bearing chiral auxiliaries, diastereoselective variants of the intra- and intermolecular reactions have proved to be elusive. As understanding of methods to control the stereochemical outcome of reactions of electron-deficient reactive intermediates develops, new opportunities to develop substrate- or catalyst-controlled variants of the transformations described here may arise.

4. Experimental

4.1. General methods

All reactions were carried out in oven-dried round-bottomed flasks or Schlenk tubes. The flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of argon unless otherwise noted. Stainless-steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was carried out using neutral silica gel (Silicycle) or basic activated alumina gel (Sigma–Aldrich). All solvents were dried under argon with a solvent-purification system equipped with columns of activated alumina (Innovative Technology, Inc.). Commercial reagents were purchased from Sigma–Aldrich, Alfa Aesar, or Lancaster, and used as received. Starting materials were prepared by literature procedures (see Supplementary data). ^{1}H and ^{13}C NMR were recorded by using Varian Mercury 300- and 400-MHz spectrometers. Chemical shifts are reported in parts per million relative to TMS, and referenced to residual protium in the solvent ($CHCl_3$: δ=7.25) or the carbon resonances of the solvent ($CDCl_3$ δ=77.0). IR spectra were recorded on a Perkin–Elmer Spectrum 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory (intensity, s: strong, m: medium, w: weak). HRMS was conducted on a VG 70–250S (double focusing) spectrometer at 70 eV (EI), an AB/Sciex QStar spectrometer (ESI) or an AccuTOF JMS-T100LC (DART) spectrometer.

4.2. General procedure for preparation of α-bromoamides

To a stirred solution of α-bromophenylacetic acid (1 equiv), the appropriate amine (1 equiv), and 4-(dimethylamino)pyridine (DMAP, 10 mol %) in dichloromethane (DCM) (0.2 M) was added *N,N′*-diisopropylcarbodiimide (DIC, 1.1 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h (or until the reaction was judged complete by TLC), then diluted with DCM and quenched with water. The resulting solution was extracted twice with DCM, and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified using flash chromatography.

*4.2.1. 2-Bromo-N,N-diethyl-2-phenylacetamide (**3b**).* The general procedure was carried out on 3.0 mmol scale, using α-bromophenylacetic acid (645 mg, 1 equiv), diethylamine (310 μL, 3.0 mmol, 1 equiv), DMAP (37 mg, 0.30 mmol, 10 mol %), and DIC (511 μL, 3.3 mmol, 1.1 equiv). After 24 h at room temperature, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in *n*-pentane) yielding the title compound as a colorless oil (405 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57–7.55 (m, 2H), 7.38–7.32 (m, 3H), 5.67 (s, 1H), 3.44–3.29 (m, 4H), 1.18 (t, 3H, J=7.2 Hz), 1.16 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 137.0, 129.1, 129.0, 128.9; IR (cm^{-1}, neat) 2973 (m), 1651 (s), 1431 (m). HRMS (ESI, M+H) calcd for $C_{12}H_{17}BrNO$: 270.0488, found 270.0480.

4.3. General procedure for intermolecular Friedel–Crafts reactions of α-halocarbonyl compounds

A stirred solution of silver salt (0.15 mmol) in DCM (0.2 mL) was cooled to −78 °C under a positive pressure of argon and then the nucleophile (0.30 mmol) was added dropwise. A solution of the α-bromoester or -amide (0.10 mmol) dissolved in DCM (0.2 mL) was added dropwise and the walls of the reaction tube were washed with an additional portion of DCM (0.1 mL): the total reaction concentration was 0.2 M. The reaction mixture was allowed to warm to room temperature over 20 h, diluted with DCM and filtered through a plug of Celite to remove the precipitated silver bromide and other silver salts. Flash chromatography (*n*-pentane/EtOAc, 19:1 then 9:1) afforded the pure product as a colorless oil or solid.

*4.3.1. Methyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (**4a**).* The general procedure was carried out on 0.10 mmol scale, using methyl 2-bromo-2-phenylacetate (16 μL, 0.10 mmol), silver trifluoromethanesulfonate (39 mg, 0.15 mmol, 1.5 equiv), and 1-methylindole (37 μL, 0.30 mmol, 3 equiv). After 20 h at room temperature, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (3% EtOAc in *n*-pentane) yielding the title compound as a colorless oil (26 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.48–7.43 (m, 3H), 7.36–7.29 (m, 4H), 7.27–7.20 (m, 1H), 7.11–7.06 (m, 2H), 5.28 (s, 1H), 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 139.0, 137.3, 128.8, 128.8, 128.7, 128.6, 128.1, 127.5, 127.3, 122.1, 119.5, 119.3, 112.3, 109.6, 52.5, 49.0, 33.0; IR (cm^{-1}, neat) 2949 (m, br), 1732 (s). HRMS (EI) calcd for $C_{18}H_{17}NO_2$: 279.1259, found 279.1261.

4.4. General procedure for intramolecular Friedel–Crafts reactions of α-halocarbonyl compounds

A stirred solution of silver salt (0.23 mmol) in DCM (0.3 mL) was cooled to −78 °C under a positive pressure of argon and then 2-bromo-2-phenylacetamide (0.15 mmol) in DCM (0.3 mL) was added dropwise. The walls of the reaction tube were washed with an additional portion of DCM (2.4 mL): the total reaction concentration was 0.05 M. The reaction mixture was allowed to warm to room temperature and stirred for 20 h, diluted with DCM and filtered through a plug of silica to remove the precipitated silver bromide and other silver salts. Flash chromatography afforded the pure product as a colorless solid or oil.

*4.4.1. 2-Methyl-4-phenyl-1,2-dihydroisoquinolin-3(4H)-one (**7c**).* General procedure C described was carried out on 0.15 mmol scale, using *N*-benzyl-2-bromo-*N*-methyl-2-phenylacetamide (48 mg, 0.15 mmol) and silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv). After 20 h at room temperature, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (30% EtOAc in *n*-pentane) yielding the title compound as a yellow solid (29 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32–7.21 (m, 6H), 7.14–7.12 (m, 3H), 4.88 (s, 1H), 4.68 (d, 2H, J=15.9 Hz), 4.35 (d, 2H, J=15.9 Hz), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 139.1, 135.8, 131.7, 128.9, 128.2, 128.1, 127.9, 127.3, 127.3, 125.5, 52.8, 52.7, 35.2; IR (cm^{-1}, neat) 2927 (m), 1625 (s), 1495 (m). HRMS (EI, M^+) calcd for $C_{16}H_{15}NO$: 237.1154, found 237.1154.

Acknowledgements

This work was funded by grants from NSERC (Discovery Grants Program), the Canadian Foundation for Innovation, and the Province of Ontario.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.065.

References and notes

1. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.
2. (a) Fu, G. C.; Lundin, P. M. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029; (b) Fu, C. G.; Lou, S. *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011; (c) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266; (d) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303; (e) Studte, S.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455; (f) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787; (g) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889; (h) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240–10241.
3. (a) Witek, J. A.; Weinreb, S. M. *Org. Lett.* **2011**, *13*, 1258–1260; (b) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *11*, 53–73; (c) See also Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546–4547; (d) Miyoshi, T.; Miyakawa, T.; Ueda, M.; Miyata, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 928–931.
4. (a) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857–12869; (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560 and references cited therein.
5. (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–3945; (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–2465; (c) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151–4162; (d) Bégué, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207–212; (e) Creary, X. *Chem. Rev.* **1991**, *91*, 1625–1678.
6. Takeuchi, K.; Yoshida, M.; Ohga, Y.; Tsugeno, A.; Kitagawa, T. *J. Am. Chem. Soc.* **1990**, *55*, 6063–6065.
7. (a) Ogata, Y.; Ishiguro, J.; Kitamura, Y. *J. Org. Chem.* **1951**, *16*, 239–242; (b) Baudry, D.; Charpentier-Morize, M. *Tetrahedron Lett.* **1973**, *32*, 3013–3016; (c) De Kimpe, N.; Verhe, R.; De Buyck, L.; Schamp, N.; Charpentier-Morize, M. *Tetrahedron Lett.* **1982**, *23*, 2853–2856; (d) Cambillau, C.; Charpentier-Morize, M. *J. Chem. Soc., Chem. Commun.* **1982**, 211–212; (e) Kulkarni, G. C.; Karmarkar, S. N.; Kelkar, S. L.; Wadia, M. S. *Tetrahedron* **1988**, *16*, 5189–5198; (f) Philippe, N.; Denivet, F.; Vasse, J.-L.; Santos, J. S. O.; Levacher, V.; Dupas, G. *Tetrahedron* **2003**, *59*, 8049–8056.
8. (a) Harmata, M. *Chem. Commun.* **2010**, 8886–8903; (b) Harmata, M. *Chem. Commun.* **2010**, 8904–8922.
9. Smith, A. G.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 1784–1787.
10. Lai, P.-S.; Taylor, M. S. *Synthesis* **2010**, *9*, 1449–1452.
11. Lewis acids that provided inferior yields included $MeAlCl_2$, Me_2AlCl, $TiCl_4$, $ZnBr_2$, Me_3SiCl, $FeCl_3$, $BiCl_3$, $InCl_3$, and $Sc(OTf)_3$.
12. For examples of experimental evidence suggesting a role for cation–π or cation–*n* interactions in synthetic processes: (a) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032; (b) Katz, C. E.; Ribelin, T.; Withrow, D.; Basseri, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 3318–3327; (c) Ribelin, T.; Katz, C. E.; Withrow, D.; Smith, S.; Manukyan, A.; Day, V. W.; Beuenswander, B.; Poutsma, J. L.; Aubé, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6233–6235; (d) Yao, L.; Aubé, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766–2767; (e) Yamada, S. *Org. Biomol. Chem.* **2007**, *5*, 2903–2912 and references cited therein; (f) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227; (g) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184–8185; (h) Lakshminarasimhan, P.; Bunoj, R. B.; Chandresekhar, J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 4815–4816.
13. (a) Brown, D. S.; Earle, M. J.; El Gihani, M. T.; Heaney, H. *Synlett* **1995**, 269–271; (b) Earle, M. J.; Heaney, H. *Synlett* **1992**, 745–747.
14. (a) Rubenbauer, P.; Bach, T. *Chem. Commun.* **2009**, 2130–2132; (b) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10106–10109; (c) Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Bal, R. G.; Tsou, N. N. *Org. Lett.* **2008**, *10*, 3037–3040; (d) Stadler, D.; Bach, T. *Chem.—Asian J.* **2008**, *3*, 272–284; (e) Mühlthau, F.; Stadler, D.; Goeppert, A.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668–9675; (f) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348–9349.
15. Calculations were carried out using Gaussian 09. See the Supplementary data for details.
16. Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964.
17. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.
18. Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32.
19. (a) Amoroso, R.; Bettoni, G.; De Filippis, B.; Tricca, M. L. *Chirality* **1999**, *11*, 483–486; (b) Song, C. E.; Lee, S. G.; Lee, K. C.; Kim, I. O.; Jeong, J. H. *J. Chromatogr., A* **1993**, *654*, 303–308.
20. Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123–1126.