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Ti/Ni-Mediated Inter- and Intramolecular Conjugate Addition of Aryl and Alkenyl Halides and Triflates

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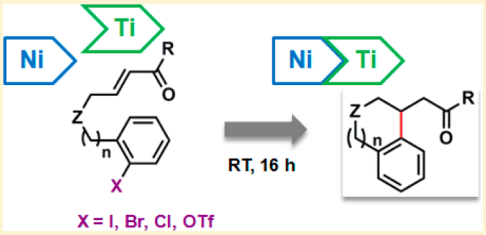
Supporting Information

ABSTRACT: In this work, we show that the unique combination of a nickel catalyst and Cp_2TiCl allows the direct conjugate addition of aryl and alkenyl iodides, bromides, and to a lesser extent, chlorides and triflates to α,β-unsaturated carbonyls at room temperature, without requiring the previous formation of an organometallic nucleophile. The reaction proceeds inter- and intramolecularly with good functional group compatibility, which is key for the development of free protecting group methodologies. Carbo- and heterocycles of five- and six-membered rings are obtained in good yields. Moreover, some insights about the mechanism involved have been obtained from cyclic voltammetry, UV−vis, and HRTEM measurements.



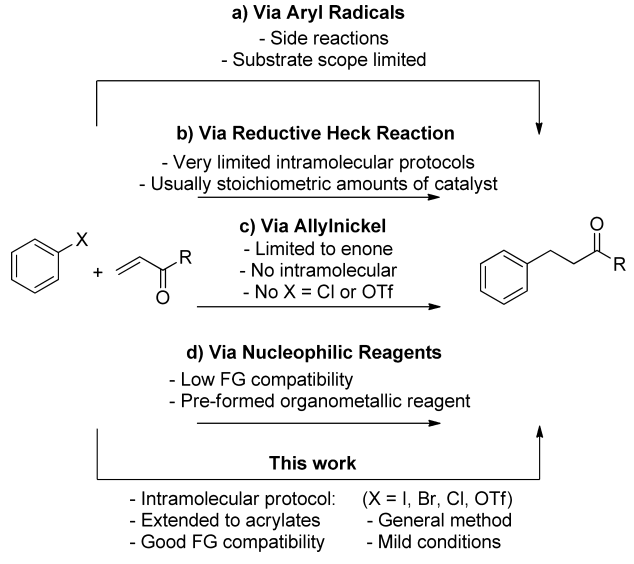
INTRODUCTION

The radical conjugate addition constitutes an important transformation in organic synthesis. It is known that nucleophilic radicals generated from organic halides with *n*-Bu_3SnH can react with electron-deficient alkenes.[1] However, phenyl and vinyl radicals are highly reactive,[2] and side reactions are of greater concern, giving addition products in only modest yields. Moreover, initiation reaction typically requires a radical initiator combined with high temperatures or irradiation.

It is worth noting that easily prepared triflates are not yet suitable starting materials in these radical transformations. An interesting alternative is the use of metal-based single-electron-transfer (SET) reagents such as SmI_2. Nevertheless, the use of SmI_2 is mainly restricted to conjugative addition reaction of alkyl halides to α,β-unsaturated esters and amides.[3,4] Although the use of aryl halides in SmI_2-mediated conjugative cyclizations has also been demonstrated, it is restricted to the formation of oxindoles.[5] Therefore, a method for the direct conjugate addition of aryl and alkenyl iodides and bromides to a variety of conjugated carbonyl compounds with high functional-group compatibility and wide substrate scope would be valuable in organic synthesis.

The reductive Heck reaction represents an alternative to this radical conjugate addition because identical final products are obtained in both reactions. Even though the Mizoroki−Heck reaction has been extensively studied, the reductive conjugative addition has received much less attention (Scheme 1, path b).[6,7] Building upon the pioneering works of the Cacchi group,[8,9] the Pd-catalyzed intermolecular conjugate addition of aryl and vinyl halides has been developed. Nevertheless, most of the protocols were restricted to the use of enones or enales[8−10] and β-nitrostyrenes.[11] The use of α,β-unsaturated esters as electrophiles is still very limited and to the best of our knowledge is restricted to only one example of intermolecular addition, yielding mixtures with nonreductive Heck coupling product.[12] Remarkably, the corresponding intramolecular Pd-catalyzed conjugated addition is limited to the use of enones as activated alkenes[13−15] for the synthesis of five-membered carbocycles at high temperatures[15] while the intramolecular Pd-catalyzed conjugated addition to α,β-unsaturated esters of

Scheme 1. Different Approaches to Conjugate Addition Reactions



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amides has not been reported. On the other hand, intermolecular conjugative addition of vinyl triflates has also been shown,[12] but it is strongly dependent on the nature of the β-substituted-α,β-unsaturated carbonyl compound, and mixtures with Heck type products are obtained. It has also been shown by Gosmini that cobalt catalysts can efficiently promote the direct conjugate addition of aryl halides and triflates onto activated olefins.[16,17] Trapping of the metal enolate by an aldehyde has also been used in domino reactions.[18,19] It is noteworthy that the intramolecular protocol has not been reported in any case.

Nickel-mediated reductive Heck reactions have also been described. Intermolecular conjugative additions of aryl and alkenyl halides to activated carbonyls have been reported involving final protonation of the resulting nickel enolate.[20−25] These protocols are usually restricted to the intermolecular coupling of aryl bromides with acrylates at high temperatures. Trapping of the nickel enolate by an aldehyde or by silicon reagents has been described by Montgomery[26,27] and Weix,[28,29] respectively. Interestingly, in this latter case, Weix has also recently demonstrated that the addition proceeds via an allylnickel intermediate,[29] describing the first catalytic application of the use of allylnickel(II) reagents previously reported by Mackenzie.[30,31] Nevertheless, this approach based on allylnickel intermediates is still limited to the intermolecular coupling of enones or enals as activated alkenes (Scheme1, path c). Ni-catalyzed intramolecular conjugative additions are restricted to the reported coupling of a vinyl halide to an enone,[32] an enal,[33]or an acrylate[34] in three isolated examples employed in natural product synthesis. Furthermore significant excess of $Ni(cod)_2$ catalyst (1.5−6 equiv) was necessary in all cases. To the best of our knowledge, Ni-catalyzed intramolecular reductive conjugative addition of aryl halides has not been described.

Direct conjugate addition of aryl and vinyl organometallic reagents to α,β-unsaturated carbonyls constitutes other important transformation in organic synthesis, yielding similar final products. In this context, the use of copper salts has been widely described for conjugate additions from Grignard or lithium derivatives (Scheme 1, path d).[35] Nevertheless, limited functional-group compatibility has motivated the use of other transition-metal catalysts, such as rhodium[36] or palladium,[37] combined with more convenient addition of less reactive carbon nucleophiles, such as organozinc,[38,39] organozirconium,[40] or organoborane[41] compounds. These strategies represented an enormous progress in this field, expanding the scope of the reaction and improving FG tolerance. Nevertheless, the main weakness of those protocols is still the required preformed organometallic reagents, and functional group tolerance remains a challenge despite the advances reported so far. Although some metalated nucleophiles, especially boronic acid and derivatives, are easy to handle and prepare or commercially available, they are generally synthesized from the corresponding aryl halides, and consequently, extra synthetic steps might be necessary. Therefore, the direct use of aryl halides presents important benefits regarding experimental conditions and structural variety.

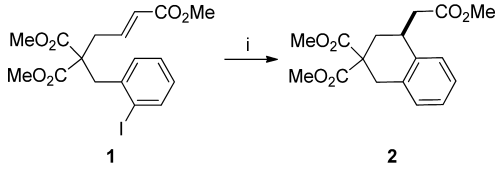
Herein, we report a novel catalytic strategy which allows the direct inter- and intramolecular conjugate addition of aryl and alkenyl iodides and bromides to acrylates without requiring the previous formation of an organometallic nucleophile. Both good functional-group compatibility and wide substrate scope are displayed. The method is based on the unique combination of a Ni catalyst with a Lewis acid such as Cp_2TiCl. The first general intramolecular protocol is described giving rise to carbo- and heterocycles of five- and six-membered rings. Noteworthy, the coupling of aryl chlorides and triflates under mild conditions is also demonstrated. Finally, a general mechanism for the reductive conjugate addition is presented.

RESULTS AND DISCUSSION

Initially, we explored the feasibility of using the combination of a Pd or Ni catalyst with the unique features of Cp_2TiCl,[42−47] a SET reagent which can also act as a very efficient Lewis acid.[48,49] Procedures based on palladium/titanium combination have proven to be capable of promote allylation,[50] crotylation, prenylation,[51] and propargylation[52] of carbonyl compounds, as well as Michael-type addition[53] using allylic carbonates as pronucleophiles. Oppolzer-type[46] as well as Heck and reductive-type cyclizations[54] of alkyl iodides have also been afforded by nickel/titanium-base procedures. These hybrid organometallic-radical protocols have shown good FG tolerance and broad substrate scopes since mild reaction conditions are employed.[55,56]

First, when model compound **1** was treated with the combination $NiCl_2/PPh_3$ and Cp_2TiCl, generated in situ from the mixture Cp_2TiCl_2 and Mn dust, cyclic compound **2** was isolated in 72% (Scheme 2). However, when $PdCl_2$ was used

Scheme 2. Model Reaction[a]



1 2

[a]Reaction conditions: (i) **1** (1.0 mmol), Cp_2TiCl_2 (1.0 mmol), Mn (8.0 mmol), $NiCl_2$ (0.2 mmol), PPh_3 (0.4 mmol), TMSCl (4.0 mmol), THF, rt, 16 h, 72%.

instead of $NiCl_2$, the expected Heck-type cyclization product was obtained. In this latter case, β-hydride elimination is fast and makes this strategy not suitable for the reductive conjugate addition. Therefore, the next studies focused on the Ti/Ni combination.

Our initial experiments began with a study of the reagents directly involved in the reaction shown above. After a sequence of control experiments in which each reagent was removed, it was clear that Ni catalyst is indispensable (Table 1, entry 2). Moreover, as in all reductive couplings/additions, an electron source is required. In this case Mn was used as reducing agent

Table 1. Control Experiments

entry	Cp_2TiCl_2 (equiv)	$NiCl_2$ (equiv)	PPh_3 (equiv)	yield[a] (%)
1	1.0	0.2	0.4	72
2	0.7		0.4	0
3		0.2	0.4	∼10
4		2.0	4.0	55
5	0.7	0.2		61
6	0.7	0.2	0.4	0[b]
7	0.7	0.2	0.4	0[c]

[a]Yields correspond to isolated products after chromatographic purification. [b]Mn dust was not added in this case. [c]Me_3SiCl was not used in this case.

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(Table 1, entry 6). Finally, Me_3SiCl was also necessary (Table 1, entry 7). Lack of one of these individual components yielded starting iodide **1**. Interestingly, we found that the presence of Cp_2TiCl is very beneficial for the yield of the reaction (Table 1, entry 3).

The required amount of the metal catalysts was optimized using the model reaction shown in Scheme 2. The results outlined in Table 2 show that the amount of both Cp_2TiCl_2 and $NiCl_2$ can be considerably reduced to 0.2 and 0.1 equiv, respectively (Table 2, entry 5). However, the best yield was obtained by using Cp_2TiCl_2 in 0.7 and $NiCl_2$ in 0.2 equiv amounts; therefore, we considered those as the optimal conditions to be used (Table 2, entry 2). The reaction run with Zn instead of Mn as co-reductor was also tested, although cyclic compound **2** was obtained in lower yield (Table 2, entry 7).[57]

Table 2. Optimization of Metal Catalyst Loading

entry	Cp_2TiCl_2 (equiv)	$NiCl_2$ (equiv)	yield[a] (%)
1	1.0	0.2	72
2	0.7	0.2	76
3	0.5	0.2	63
4	0.2	0.2	54
5	0.2	0.1	50
6	0.7	0.1	64
7	0.7	0.2	57[b]

[a]Reactions were run in combination with **1** (1.0 equiv) PPh_3 (0.4 equiv), Mn (8 equiv), Me_3SiCl (4 equiv), THF, rt, 16 h. Yields correspond to isolated products after purification. [b]Zn (8 equiv) was added in this case instead of Mn dust.

A variety of Ni catalysts and ligands were also tested with model compound **1**, and the results are summarized in Table 3.

Table 3. Ligand and Ni Catalyst Effects

entry	[Ni] cat. (equiv)	ligand (equiv)	yield[a] (%)
1	$NiCl_2$ (0.2)	PPh_3 (0.4)	76
2	$NiCl_2$ (0.2)	PCy_3 (0.4)	45
3	$NiCl_2$ (0.2)	dppe (0.2)	51
4	$NiCl_2$ (0.2)	$P(OPh)_3$ (0.4)	0
5	$NiCl_2$ (0.2)	bipy (0.2)	0
6	$NiCl_2(PPh_3)_3$ (0.2)		69
7	$Ni(acac)_2$ (0.2)	PPh_3 (0.4)	78
8	$NiCl_2$(glyme) (0.2)		68
9	$NiCl_2$(dppe) (0.2)		5
10	$NiCl_2(PtBu_3)$ (0.2)		31
11	$NiBr_2$ (0.2)	PPh_3 (0.4)	69
12	$Ni(cod)_2$ (0.2)	PPh_3 (0.4)	77

[a]Reactions were run in combination with **1** (1.0 equiv) Cp_2TiCl_2 (0.7 equiv), Mn (8 equiv), Me_3SiCl (4 equiv), THF, rt, 16 h. Yields correspond to isolated products after purification.

Although the phosphorus ligand does not seem to be strictly required in this transformation (Table 1, entry 5), it might help in stabilizing low-valence nickel intermediates. Different phosphines could be used, including mono- and bidentate ligands. Nevertheless, the best yields were obtained with PPh_3 (Table 3, entries 1, 7, 11, and 12). On the other hand, neither phosphites nor pyridine derivatives were suitable ligands for this transformation (Table 3, entries 4 and 5). Interestingly, preformed catalyst $[NiCl_2(PPh_3)_2]$ gave a lower yield than the combination $NiCl_2/PPh_3$ (Table 3, entry 1 versus 6), which suggests that reduction of the preformed complex to the active Ni(0) species is slightly disfavored. Similar results were obtained when the reaction was performed with $NiCl_2$, $Ni(acac)_2$ or $Ni(cod)_2$ as nickel source (Table 3, entries 1, 7, and 12).

Good functional-group compatibility is a key element when it comes to the development of cyclization reactions. The features displayed by the protocol presented here make it ideal for an intramolecular protocol considering that it avoids preformed metalated nucleophiles. In this case, the compulsory polyfunctionalized compounds can be easily prepared.[58] As shown in Table 4, the intramolecular reductive coupling of aryl iodides, bromides, chlorides, and even triflates to α,β-unsaturated esters has been developed. Thus, when polyfunctionalized substrates **1**, **3**, **4**, and **5** were submitted to optimized reaction conditions, cyclic compound **2** was obtained in good yield in all cases (Table 4, entries 1−4). Noteworthy, the intramolecular addition of aryl bromides, chlorides, and triflates to unsaturated carbonyls can be conducted at room temperature. To the best of our knowledge, this result (entry 4) constitutes the first example of an intramolecular reductive coupling of an aryl triflate.

The intramolecular reductive coupling of aryl derivatives to activated alkenes, including α,β-unsaturated esters (entries 1−9), ketones (entry 10), and amides (entries 11 and 12), allows the synthesis of different benzo-fused carbo- and heterocycles at room temperature having different electronic and steric profiles with moderate to good yields. Thus, the reaction takes place with electron-rich pronucleophiles as phenylsulfonamides (entries 7, 8, 11, and 12), as well as with benzylsulfonamides (entry 9) and benzylalkanes (entries 1−6 and 10). Moreover, the reaction proceeds well to give cycles of six (entries 1−6, 9, and 10) and five members (entries 7, 8, 11, and 12).[59] Remarkably, this method allows an easy access to nitrogen-containing heterocycles structurally related with alkaloids such as dihydroindoles **10**, tetrahydroisoquinolines **13**, and dihydroindolones **17**. Those benzo-fused nitrogen heterocyclic systems are of significant interest as potential pharmaceutical agents due to their action as enzyme inhibitors, receptor ligands, and hormone release promotors.[60−62]

Subsequently, intermolecular coupling of aryl halides with acrylates was tested under optimized conditions (Scheme 3). First, the coupling of iodobenzene with methyl acrylate was examined. Despite the potential for many undesired competing reactions such as the direct aryl halide reduction, acrylate reduction, or Heck coupling, the reaction was very clean, affording the desired reductive conjugate addition product **19** in 61% yield after 16 h at room temperature (Chart 1). A considerable excess of methyl acrylate was advisable as better yields were observed.[63] A variety of activated alkenes was tested as reaction partners with iodobenzene, and although acrylonitrile, 5,6-dihydro-2*H*-pyran-2-one, and *tert*-butyl acrylate were coupled (Chart 1, compounds **20**−**22**), the best result was obtained with methyl acrylate (Chart 1, **19**). When unfunctionalized alkenes such as styrene or substituted methyl crotonate were used, coupling products were not observed.[58] The results suggest that an appropriate coordination to the activated alkene is required.

The scope of this process appears to be broad as the aryl iodide might also be functionalized with ethers, bromides, chlorides, tosylates, acetates, esters, silanes, or amides (Chart 2). Further FG tolerance is also demonstrated as derivatives

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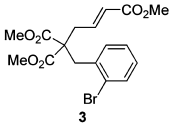
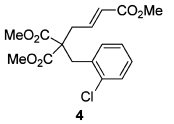
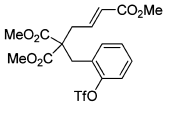
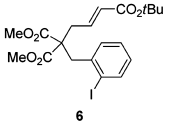
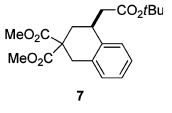
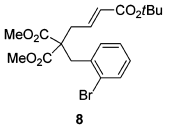
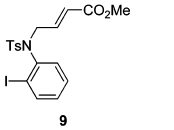
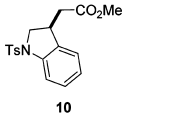
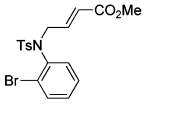
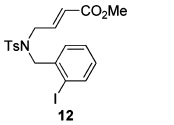
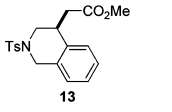
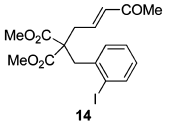
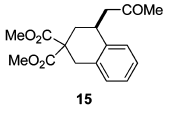
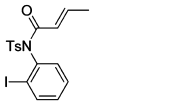
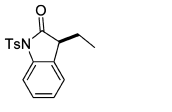
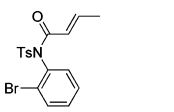
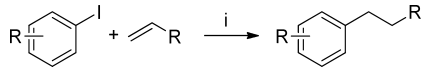
Table 4. Ti/Ni-Catalyzed Intramolecular Reductive Addition[a]

Entry	Starting Material	Product	Yield (%)
1	**1**	**2**	72
2	 **3**	**2**	63
3	 **4**	**2**	71
4	 **5**	**2**	77
5	 **6**	 **7**	58
6	 **8**	**7**	56
7	 **9**	 **10**	73
8	 **11**	**10**	34
9	 **12**	 **13**	58[b]
10	 **14**	 **15**	51
11	 **16**	 **17**	55
12	 **18**	**17**	48

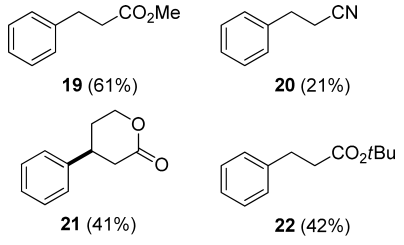
[a]Reaction and conditions: polyfunctionalized substrate (1.0 equiv), Cp_2TiCl_2 (0.7 equiv), $NiCl_2$ (0.2 equiv), PPh_3 (0.4 equiv), Mn (8 equiv), Me_3SiCl (4.0 equiv), THF, rt, 16 h. [b]Compound **13** was isolated as a 5:1 mixture with reduced compound methyl 4-(*N*-benzyl-4-methylphenylsulfonamido) butanoate.

Scheme 3. General Intermolecular Reaction of Aryl Iodides and Activated Alkenes[a]



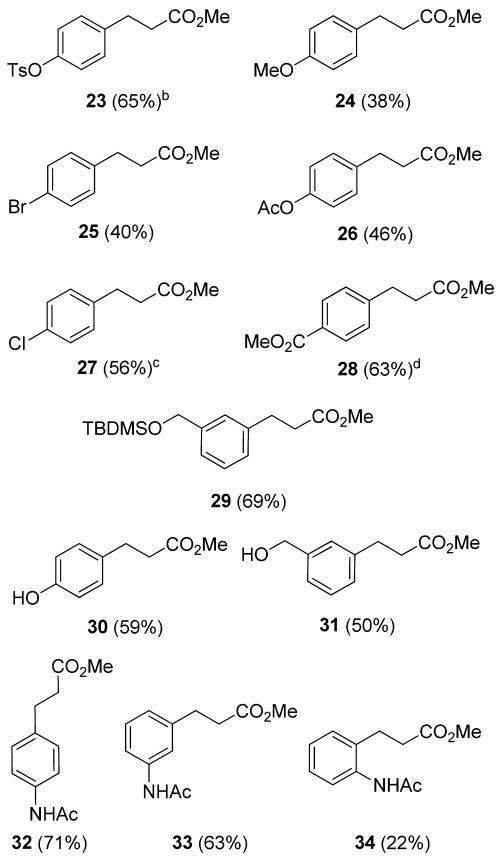
[a]Reaction and conditions: (i) aryl iodide (1.0 equiv), acrylate (10 equiv), Cp_2TiCl_2 (0.7 equiv), $NiCl_2$ (0.2 equiv), PPh_3 (0.4 equiv), Mn (8 equiv), Me_3SiCl (4.0 equiv), THF, rt, 16 h.

Chart 1. Products and Yields Obtained from Iodobenzene



19 (61%) **20** (21%) **21** (41%) **22** (42%)

Chart 2. Products and Yields Obtained from Aryl Iodides and Methyl Acrylate[a]



23 (65%)[b] **24** (38%) **25** (40%) **26** (46%) **27** (56%)[c] **28** (63%)[d] **29** (69%) **30** (59%) **31** (50%) **32** (71%) **33** (63%) **34** (22%)

[a]Yields correspond to isolated products after purification. [b]Compound **23** was isolated as a 10:1 mixture with methyl 3-(4-tosylphenyl)-acrylate. [c]Compound **27** was isolated as a 10:1 mixture with methyl 3-(4-chlorophenyl)acrylate. [d]Compound **28** was isolated as a 15:1 mixture with methyl 3-(4-carboxymethylphenyl)acrylate.

bearing a free OH are accepted (compounds **30** and **31**), which represents a notable improvement compared to described methods base on nucleophilic aryl reagents. It is noteworthy that reactions with *meta*- and *ortho*-substituted aryl iodides yielded coupling products **29**, **31** or **33**, and **34**, respectively.

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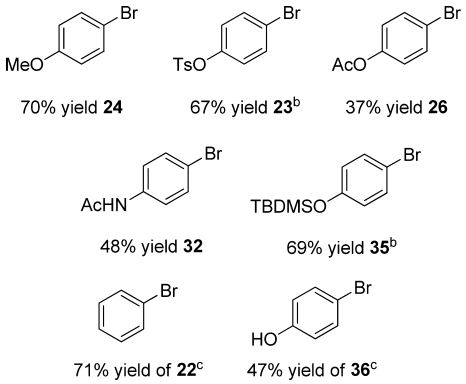
However, lower yields are observed from *ortho*-substituted aryl halides showing that the steric hindrance at the organic halide plays a special role in the reaction pathway.

The lower reactivity of bromobenzene compared to iodobenzene enabled the chemoselective coupling of 4-bromo-1-iodobenzene (Chart 2, compound **25**). Interestingly, unlike the intramolecular protocol, the intermolecular addition of aryl bromides to unsaturated carbonyls required heating the reaction mixture at 50 °C.[64] Furthermore and despite of the harsher conditions employed, notable functional group compatibility is again displayed as ethers, tosylates, acetates, silanes, amides, or free alcohols are tolerated (Chart 3).

Chart 3. Aryl Bromides Used and Yields Obtained[a]



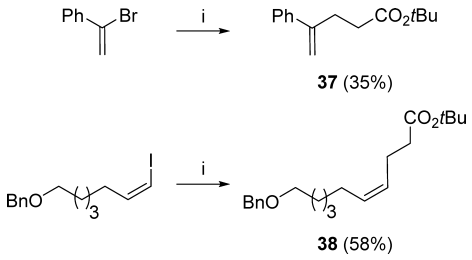
[a]Yields correspond to isolated products after purification. [b]Yield based on recovered starting material. [c]*tert*-Butyl acrylate was used in this case.

The steric hindrance plays an important role not only at the organic halide but also at the activated alkene, as *β*-substituted alkenes do not afford any intermolecular addition product. An initial coordination of acrylate to Ni(0) seems necessary.[58] In the intramolecular protocol, probably due to the proximity between the reactive centers induced by the substrate structure, subsequent oxidative addition and formation of the new C−C bond are easier, avoiding highly energetic intermediates.

In addition to aryl halides, alkenyl halides have also shown good reactivity. As illustrated in Scheme 4, vinyl iodides and bromides have been reductively coupled to *tert*-butyl acrylate to form products **37** and **38**.[65]

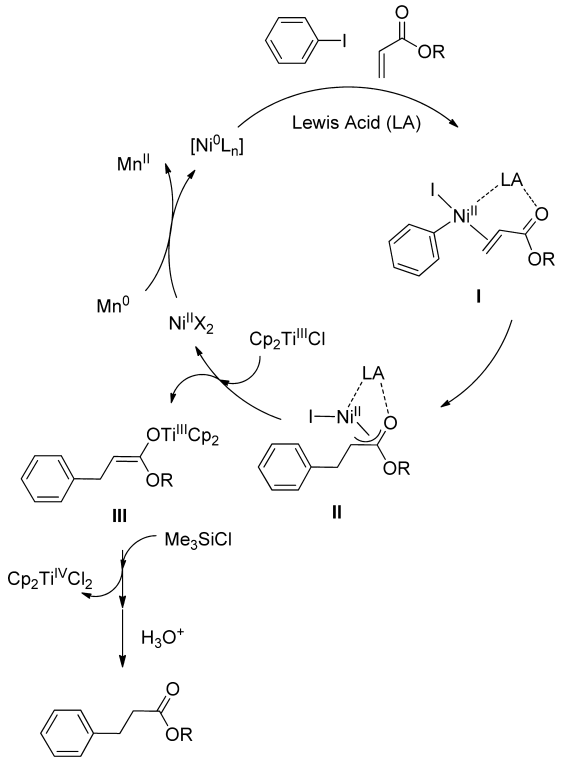
This novel Ti/Ni-mediated conjugate addition of aryl derivatives can be rationalized by the mechanism illustrated in Scheme 5. Oxidative addition of the aryl iodide to Ni(0) and

Scheme 4. Intermolecular Coupling of Vinyl Halides and *tert*-Butyl Acrylate[a]



[a]Reaction and conditions: (i) vinyl halide (1.0 equiv), *tert*butyl acrylate (10 equiv), Cp_2TiCl_2 (0.7 equiv), $NiCl_2$ (0.2 equiv), PPh_3 (0.4 equiv), Mn (8 equiv), Me_3SiCl (4.0 equiv), THF, 50 °C, 16 h.

Scheme 5. Proposed Mechanism for Intermolecular Addition of Iodobenzene to Methyl Acrylate



coordination of acrylate would generate Ni(II) complex **I**. This proposed structure is supported by the following experimental data. When model compound **1** (Scheme 2) was treated with stoichiometric amounts of a Ni(0) catalyst and Me_3SiCl as Lewis acid in the absence of Mn dust, compound **2** was isolated in 70% yield, strongly supporting that only Ni(0) species are responsible for the initial step.[66] Additionally, although external phosphorus ligands resulted in better yields (Table 2, entry 2), probably by stabilization of initial Ni(0) species, their use is not strictly required (Table 1, entry 5). Taking into account that the presence of a Lewis acid, such as Me_3SiCl or Cp_2TiCl, is mandatory and no other ligand is required, we suggest a specific coordination sphere for that Ni(II) complex **I**. This structure is also supported by the proposed intermediates for Ni-catalyzed reductive aldol addition of acrylates and aldehydes developed by Montgomery et al.[27] Consequently, the steric hindrance of both interacting partners plays a crucial role, explaining the worse reactivity of *ortho*-substituted aryl halides (Chart 2, **34**) and *β*-substituted activated alkenes.[58] On the other hand, intramolecular coupling is favored and takes place at room temperature even when less active aryl bromides, chlorides, or triflates are used as electrophiles.

Additional experiments were carried out to understand the role of phosphorus ligands. At first, we cannot rule out the interaction of phosphorus ligands with coordinative unsaturated Cp_2TiCl. To clarify this point, the UV−vis spectra of a solution of Cp_2TiCl in tetrahydrofuran (THF) were recorded. As increasing amounts of PPh_3 were added to the solutions the UV−vis spectrum of Cp_2TiCl did not change notably, suggesting that the increase in yield is exclusively owing to coordination with Ni complexes. Consequently, when the UV−vis spectra of solutions of $Ni(acac)_2$ in THF were recorded in the presence of PPh_3 they exhibited a marked alteration.[67,68]

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The subsequent proposed step is a 1,2-insertion into the α,β-unsaturated carbonyl, yielding nickel(II) enolate **II**. Instead of the usual β-hydride elimination process in the presence of Cp_2TiCl, a transmetalation takes place to produce titanium(III) enolate **III**, recovering the initial Ni(II) catalyst. Typically, as commented above, when a Pd catalyst was used, fast β-hydride elimination ended the reaction yielding β-aryl α,β-unsaturated carbonyl products by a standard Pd(0)-catalyzed Heck reaction. A following trapping of such enolate **III** with trimethylsilane chloride would liberate titanocene(III) chloride to produce a silyl enol ether,[69−71] which would lead to the final reduced product after an acidic workup.[72]

Ni(II) complexes have been extensively used in combination with Mn(0) as reductant, and therefore, initial activation of the $NiCl_2$ by Mn dust could be assumed. Nevertheless, in our case, the lack of Ti(III) required a considerable excess of nickel catalyst being, therefore, indispensable for the regeneration of active Ni(0) species. To clarify this issue, electrochemical studies were carried out on a glassy carbon working electrode (Figure 1). First, the electrochemical properties of Ti(III) and

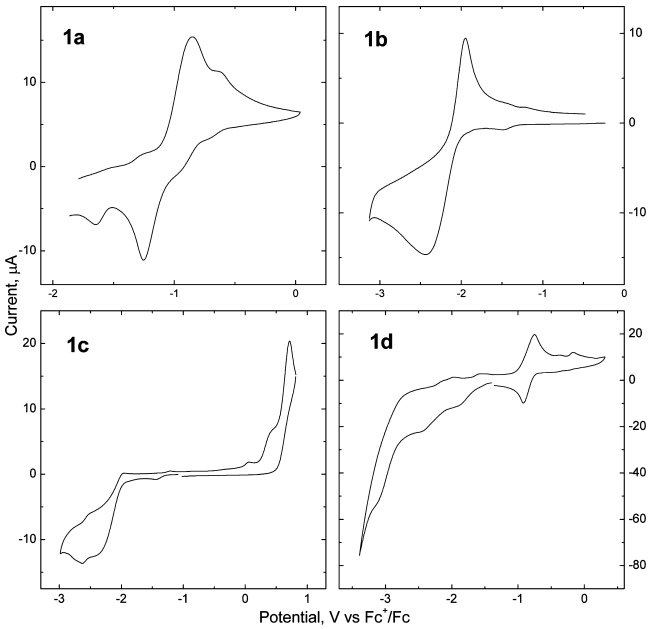

Figure 1. Cyclic voltammograms of 4 mM solutions of: (a) Cp_2TiCl; (b) $Ni(acac)_2$; (c) solution of $Ni(acac)_2$ after being treated with Mn for 50 min; (d) solution of Cp_2TiCl, $Ni(acac)_2$, and Mn; recorded at a sweep rate 0.1 V s^{-1} (a,b,d) or 0.05 V s^{-1} (c) in 0.15 M Bu_4NPF_6/THF. Fc (ferrocene) or Fc* (decamethylferrocene) were added as internal standards at the end of a short series of experiments, and potential values are reported vs Fc^+/Fc.

Ni(II) complexes were defined by cyclic and square-wave voltammetries (CV and SWV) conducted in THF solution containing 0.15 M Bu_4NPF_6 as the supporting electrolyte. Representative CVs for Cp_2TiCl and $Ni(acac)_2$ in THF solution[73] are shown in parts a and b, respectively, of Figure 1.

For $Ni(acac)_2$, a very wide reduction peak with $E_{pc} = -2.44$ V vs Fc^+/Fc at 0.1 V s^{-1} (Fc = ferrocene) is shown in CV; upon scan reversal, an oxidation peak at $E_{pa} = -1.95$ V vs Fc^+/Fc appears (Figure 1b). The very large anodic to cathodic peak separation of ca. 500 mV (ΔE_p for Fc and Fc*, decamethylferrocene, standards in the same solution was close to 100 mV) as well as the general CV shape indicate that the process is not a simple reversible one. Accordingly, in SWV the reduction process is composed by a large peak at $E_p = -2.14$ V followed by a smaller one at $E_p = -2.63$ V vs Fc^+/Fc (Figure 2, solid line). In our hands, the potential for Cp_2TiCl

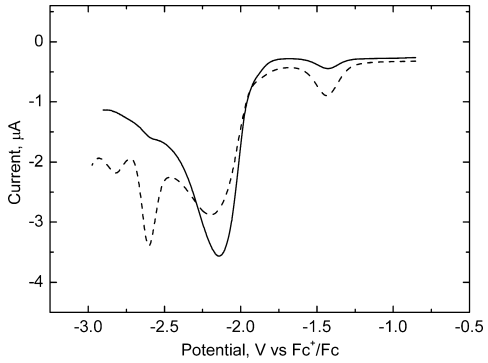

Figure 2. Square wave voltammograms of 4 mM solutions of $Ni(acac)_2$ (solid line) and $Ni(acac)_2$ after being treated with Mn for 50 min (dashed line). Data recorded at 15 Hz in 0.15 M Bu_4NPF_6/THF.

solution oxidation was $E_p = -0.89$ V vs Fc^+/Fc as measured from SWV, similar to the previously reported value[74] and supporting that Cp_2TiCl is probably incapable of reducing $Ni(acac)_2$.

The reduction of Mn(II) complexes occurs at more negative potentials compared to the Ni(II) complexes, and therefore the reduction of Ni(II) by Mn(0) is expected.[75] Experimentally, after treatment of $Ni(acac)_2$ with Mn(0) as stoichiometric reducing agent in THF for 50 min at room temperature, the CV was recorded (Figure 1c). Again, the cathodic scan showed two close reduction waves, which are partially reversible in CV and gave rise to peaks at −2.19 V and −2.61 V vs Fc^+/Fc in SWV. However, in this case the second reduction wave becomes a clear peak in the presence of Mn (Figure 2, dashed line), supporting that Mn(0) had reduced some of the initial Ni(II). Lastly, in Figure 1d, CV for $Ni(acac)_2$ in THF changed drastically upon addition of Cp_2TiCl. The typical CV pattern of the Ni complex was no longer present, indicative of ligand exchange between the complexes.[76] In addition, as shown above (Figure 1a), the cyclic voltammogram of Cp_2TiCl complex is mainly characterized by irreversible waves. However, as can be seen in Figure 1d, in the presence of $Ni(acac)_2$, a process corresponding to the full reversible Ti(III/IV) oxidation is exhibited at $E_{1/2} = -0.85$ V vs Fc^+/Fc. Moreover, we observed the extinction of this Ti peak as long as a black precipitate was formed in the cell. This result indicates again a clear interaction between the two metal complexes.

At this point, we wondered if this solid was obtained due to the voltage applied during the experiment. Therefore, we decided to further investigate the reaction between Cp_2TiCl and $Ni(acac)_2$. In a Schlenk flask, a light green THF solution of Cp_2TiCl was treated with a THF solution of $Ni(acac)_2$ under Ar atmosphere at room temperature. An immediate color change to dark green was observed and within the next 15 min a dark gray precipitate was produced. The mixture was allowed to stand unperturbed, and a black precipitated was obtained. To inspect in deeper detail the interaction between Ti(III) and Ni(II), high-resolution transmission electron microscopy (HRTEM) was used to characterize the solid precipitate obtained. Figure 3 shows a TEM image of the isolated solid. A closer examination of the images shows that particles in the 5−

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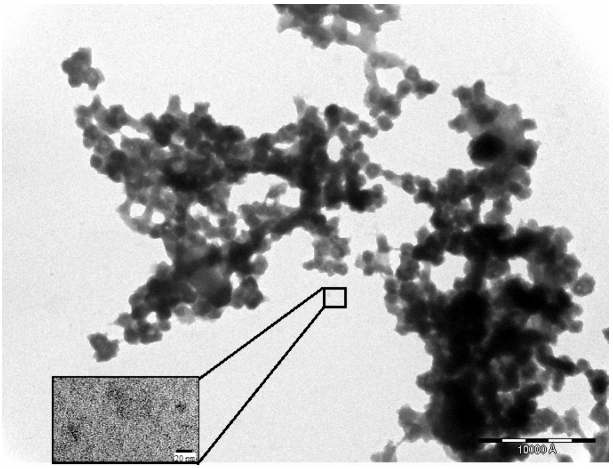

Figure 3. TEM image of particles produced upon the addition of 5 mL of $Ni(acac)_2$ in THF (4 mM) to 8 mL of Cp_2TiCl (10 mM).

10 nm range were formed. A clear aggregation was observed, and particles of 80−150 nm are shown. Moreover, EDX analysis of the particles demonstrated that the solid particles obtained are mainly constituted of nickel and are probably the source of the required Ni(0) complexes.[77]

These experimental results suggest that an initial ligand exchange between Ni(II) and Ti(III) generates a new Ni(II) complex, which can be easily reduced. The Lewis acidity of Cp_2TiCl is known, and we can assume that the ligand exchange can produce cationic Ni(II) complexes, which are now more easily reduced by Mn or by Cp_2TiCl itself. At this stage, Cp_2TiCl would present a dual role: (a) favoring the reduction of Ni(II) species back to a catalytically active Ni(0) form via its activation by a Lewis acidic interaction toward its more efficient reduction and (b) acting as an efficient Lewis acid stimulating the α,β-unsaturated carbonyl for the insertion reaction.

■ CONCLUSIONS

We have shown that the unique combination of a nickel catalyst and Cp_2TiCl allows the direct conjugate addition of aryl and alkenyl iodides, bromides, and to a lesser extent, chlorides and triflates to acrylates, without requiring the previous formation of an organometallic nucleophile. The reaction proceeds inter- and intramolecularly with good functional group compatibility, which is essential for the development of free protecting group methodologies. Remarkably, α,β-unsaturated esters and amides are suitable substrates, thus expanding the substrate scope of related Ni-mediated transformations. Moreover, some insights about the complex mechanism of this multimetallic protocol have been reported.

■ EXPERIMENTAL SECTION

General Methods. All reagents and solvents were purchased from commercial sources and used without further purification. Dry THF was freshly distilled over Na/benzophenone. Flash column chromatography was carried out using silica gel 60 (230−400 mesh, Scharlab) as the stationary phase. Analytical TLC was performed on aluminum sheets coated with silica gel with fluorescent indicator UV_{254} (Alugram SIL G/UV_{254}, Mackerey-Nagel, Germany) and observed under UV light (254 nm) and/or staining with phosphomolybdic acid solution and subsequent heating. All products were characterized by their NMR and MS spectra. All ^1H and ^{13}C NMR spectra were recorded on 300, 400, or 500 MHz spectrometers at a constant temperature of 298 K. Chemical shifts are reported in ppm and referenced to residual solvent. Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint = quintet, q = quartet, t = triplet, d = doublet, s = singlet, b = broad. Assignment of the ^{13}C NMR multiplicities was accomplished by DEPT techniques. Cyclic and square wave voltammetry (CV and SWV, respectively) experiments were performed with a three electrode cell under N_2 (>99.9995%) atmosphere at 25 °C. A Pt-mesh counterelectrode and an Ag-wire quasireference electrode were used. The working electrode was a glassy carbon disk. The solvent was THF containing 0.15 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte. All potential values in this work are referred to the Fc^{+}/Fc (Fc = ferrocene) system, as Fc or Fc* (Fc* = decamethylferrocene) was added as an internal reference after each short series of measurements. $E_{1/2} = (E_{pa} + E_{pc})/2$ of the Fc^{+}/Fc was also measured as +0.47 V vs Fc^{*+}/Fc^* in the THF solution.

Synthesis and Characterization Data of Polyfunctionalized Substrates for Intramolecular Coupling 1, 3−6, 8, 9, 11, 12, 14, 16, and 18. *Synthesis of (E)-Trimethyl 5-(2-Iodophenyl)pent-1-ene-1,4,4-tricarboxylate (**1**).* (*E*)-Methyl 4-bromobut-2-enoate (0.98 mL, 8.33 mmol) was added over a solution of dimethyl malonate (0.87 mL, 7.57 mmol) and K_2CO_3 (1255 mg, 9.08 mmol) in MeCN (15 mL). The mixture was stirred at 60 °C during 16 h. Then K_2CO_3 was filtrated, and the solvent was removed. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give (*E*)-trimethyl but-3-ene-1,1,4-tricarboxylate (690 mg, 40%) as a yellowish oil. Its spectroscopic data were identical to the reported compound.[78]

2-Iodobenzyl bromide (1.07 g, 3.59 mmol) was added to a mixture of (*E*)-trimethyl but-3-ene-1,1,4-tricarboxylate (690 mg, 2.99 mmol) and NaH (60%) (144 mg, 3.59 mmol) in DMF (15 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. The mixture was diluted with EtOAc, washed with HCl (10%), and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **1** (1048 mg, 79%) as a yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.0 Hz, 1H), 7.28−7.22 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.95−6.85 (m, 2H), 5.83 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 2H), 3.54 (s, 1H), 2.79 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (C), 166.3 (C), 143.4 (CH), 140.1 (CH), 139.2 (C), 130.2 (CH), 129.0 (CH), 128.4 (CH), 124.3 (CH), 102.9 (C), 59.1 (C), 52.8 (CH_3), 51.6 (CH_3), 43.1 (CH_2), 36.4 (CH_2). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{19}O_6I$ $[M]^+$ 446.0226, found 446.0233.

*Synthesis of (E)-Trimethyl 5-(2-Bromophenyl)pent-1-ene-1,4,4-tricarboxylate (**3**).* 1-Bromo-2-(bromomethyl)benzene[79] (391 mg, 1.56 mmol) was added to a mixture of (*E*)-methyl 5-methylhex-2-enoate (240 mg, 1.04 mmol) and NaH (60%) (63 mg, 1.58 mmol) in DMF (15 mL). The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with brine and HCl (10%), and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **3** (313 mg, 75%) as a yellowish liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.8 Hz, 1H), 7.25−7.14 (m, 2H), 7.13−7.04 (m, 1H), 6.99−6.84 (m, 1H), 5.84 (d, J = 15.6 Hz, 1H), 3.72 (s, 9H), 3.53 (s, 2H), 2.77 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 166.4 (C), 143.4 (CH), 135.6 (C), 133.3 (CH), 131.5 (CH), 128.9 (CH), 127.5 (CH), 127.0 (C), 124.4 (CH), 58.9 (C), 52.8 (CH_3), 51.6 (CH_3), 38.3 (CH_2), 36.1 (CH_2). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{19}O_6Br$ $[M]^+$ 398.0365, found 398.0364.

*Synthesis of (E)-Trimethyl 5-(2-Chlorophenyl)pent-1-ene-1,4,4-tricarboxylate (**4**).* 1-(Bromomethyl)-2-chlorobenzene (97%) (221 mg, 1.04 mmol) was added to a mixture of (*E*)-methyl 5-methylhex-2-enoate (200 mg, 0.87 mmol) and NaH (60%) (42 mg, 1.04 mmol) in DMF (6 mL). The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with HCl (10%), and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give **4** (272 mg, 88%) as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.38 (m, 1H), 7.29−7.21 (m, 3H), 7.07−6.93 (m, 1H), 5.93 (d, J = 15.6 Hz, 1H), 3.80 (s, 9H), 3.57 (s, 2H), 2.82 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 166.3 (C), 143.3 (CH), 135.3

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(C), 133.8 (C), 131.7 (CH), 129.9 (CH), 128.7 (CH), 126.8 (CH), 124.5 (CH), 58.8 (C), 52.7 (CH_3), 51.6 (CH_3), 35.9 (CH_2), 35.8 (CH_2). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{19}O_6Cl$ $[M]^+$ 354.0870, found 354.0863.

*Synthesis of (E)-Trimethyl 5-(2-(((Trifluoromethyl)sulfonyl)oxy)-phenyl)pent-1-ene-1,4,4-tricarboxylate (**5**).* Et_3N (1.14 mL, 8.19 mmol) was added to salicylaldehyde (500 mg, 4.09 mmol) in CH_2Cl_2 (10 mL), and the solution was stirred at room temperature for 10 min. Then a sample of trifluoromethanesulfonic anhydride (0.7 mL, 5.96 mmol) was slowly added to this solution. The resulting solution was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give 2-formylphenyl trifluoromethanesulfonate (860 mg, 82%) as a yellowish oil. Its spectroscopic data were identical to those for the reported compound.[80]

$NaBH_4$ (187 mg, 5.05 mmol) was added to a solution of 2-formylphenyl trifluoromethanesulfonate (860 mg, 3.37 mmol) in MeOH (20 mL). The resulting solution was monitored by TLC and stirred at room temperature until starting material disappeared (about 10 min). Then the mixture was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give 2-(hydroxymethyl)phenyl trifluoromethanesulfonate (710 mg, 83%) as a yellowish oil. Its spectroscopic data were identical to those for the reported compound.[81]

PBr_3 (0.39 mL, 4.15 mmol) was added to a solution of 2-(hydroxymethyl)phenyl trifluoromethanesulfonate (710 mg, 2.78 mmol) in Et_2O (15 mL) at 0 °C. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was quenched with cold water. Then the mixture was diluted with Et_2O, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 5:95) to give 2-(bromomethyl)phenyl trifluoromethanesulfonate (635 mg, 72%) as a yellowish oil. Its spectroscopic data were identical to those for the reported compound.[82]

2-(Bromomethyl)phenyl trifluoromethanesulfonate (500 mg, 1.56 mmol) was added to a mixture of (*E*)-methyl 5-methylhex-2-enoate (300 mg, 1.30 mmol) and NaH (60%) (63 mg, 1.58 mmol) in DMF (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give **5** (295 mg, 48%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.21 (m, 4H), 6.87−6.77 (m, 1H), 5.83 (d, J = 15.2 Hz, 1H), 3.70 (s, 6H), 3.69 (s, 3H), 3.37 (s, 2H), 2.63 (d, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (C), 166.2 (C), 148.7 (C), 142.4 (C), 132.7 (CH), 129.5 (CH), 128.6 (CH), 128.4 (CH), 125.0 (CH), 121.7 (CH), 118.6 (q, J = 320.4 Hz, CF_3), 58.3 (C), 52.9 (CH_3), 51.6 (CH_3), 35.9 (CH_2), 33.1 (CH_2). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{18}H_{19}O_9F_3S$ $[M]^+$ 468.0702, found 468.0703.

*Synthesis of (E)-1-tert-Butyl 4,4-Dimethyl 5-(2-iodophenyl)pent-1-ene-1,4,4-tricarboxylate (**6**).* 1-(Bromomethyl)-2-iodobenzene (517 mg, 1.74 mmol) was added to a mixture of dimethyl 2-allylmalonate (0.28 mL, 1.74 mmol) and NaH (60%) (84 mg, 2.09 mmol) in DMF (15 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with HCl (10%), and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give dimethyl 2-allyl-2-(2-iodobenzyl)malonate (300 mg, 45%) as a yellowish oil. Its spectroscopic data were identical to those for the reported compound.[83]

tert-Butyl acrylate (0.34 mL, 2.33 mmol) was added to a deoxygenated solution of Grubb's second-generation catalyst (7 mg, 0.008 mmol) and compound dimethyl 2-allyl-2-(2-iodobenzyl)-malonate (300 mg, 0.78 mmol) in dry CH_2Cl_2 (5 mL), and the resulting mixture was refluxed for 48 h. The solvent was removed, and the residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **6** (201 mg, 53%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.7 Hz, 1H), 7.27−7.22 (m, 1H), 7.21−7.15 (m, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.84−6.70 (m, 1H), 5.74 (d, J = 15.5 Hz, 1H), 3.72 (s, 6H), 3.54 (s, 2H), 2.77 (d, J = 7.6 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C), 165.3 (C), 141.7 (CH), 140.1 (CH), 139.3 (C), 130.2 (CH), 128.9 (CH), 128.3 (CH), 126.5 (CH), 102.9 (C), 80.4 (C), 59.0 (C), 52.7 (CH_3), 43.0 (CH_2), 36.2 (CH_2), 28.2 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{20}H_{25}O_6I$ $[M]^+$ 488.0696, found 488.0676.

*Synthesis of (E)-1-tert-Butyl 4,4-Dimethyl 5-(2-Bromophenyl)-pent-1-ene-1,4,4-tricarboxylate (**8**).* 1-Bromo-2-(bromomethyl)-benzene (654 mg, 2.62 mmol) was added to a mixture of dimethyl 2-allylmalonate (0.28 mL, 1.74 mmol) and NaH (60%) (105 mg, 2.63 mmol) in DMF (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with HCl (10%) and brine, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give dimethyl 2-allyl-2-(2-bromobenzyl)malonate (268 mg, 45%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.8 Hz, 1H), 7.32−7.19 (m, 2H), 7.15−7.06 (m, 1H), 5.97−5.72 (m, 1H), 5.27−4.97 (m, 2H), 3.75 (s, 6H), 3.53 (s, 2H), 2.69 (d, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C), 136.2 (C), 134.0 (CH), 133.1 (CH), 131.5 (CH), 128.6 (CH), 127.3 (CH), 126.0 (C), 119.1 (CH_2), 59.1 (C), 52.5 (CH_3), 37.9 (CH_2), 32.9 (CH_2).

tert-Butyl acrylate (0.30 mL, 2.04 mmol) was added to a deoxygenated solution of Grubb's second-generation catalyst (5.7 mg, 0.007 mmol) and dimethyl 2-allyl-2-(2-bromobenzyl)malonate (230 mg, 0.68 mmol) in dry CH_2Cl_2 (7 mL), and the resulting mixture was refluxed for 48 h. The solvent was removed, and the residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **8** (128 mg, 43%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 7.8 Hz, 1H), 7.32−7.19 (m, 2H), 7.17−7.05 (m, 1H), 6.89−6.72 (m, 1H), 5.78 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.55 (s, 2H), 2.77 (d, J = 7.3 Hz, 2H), 1.49 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (C), 165.3 (C), 141.6 (CH), 135.8 (C), 133.2 (CH), 131.5 (CH), 128.8 (CH), 127.4 (CH), 126.6 (CH), 126.1 (C), 80.4 (C), 58.9 (C), 52.7 (CH_3), 38.2 (CH_2), 36.0 (CH_2), 28.2 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{20}H_{25}O_6Br$ $[M]^+$ 440.0834, found 440.0829.

*Synthesis of (E)-Methyl 4-(N-(2-Iodophenyl)-4-methylphenylsulfonamido)but-2-enoate (**9**).* *N*-(2-Iodophenyl)-4-methylbenzenesulfonamide[84] (1g, 2.69 mmol) was added to a solution of NaH (60%) (161 mg, 4.03 mmol) in THF under Ar atmosphere. The resulting solution was stirred at room temperature for 1 h. Then a sample of (*E*)-methyl 4-bromobut-2-enoate (0.47 mL, 4.03 mmol) was added to this solution at 0 °C. The resulting solution was stirred at room temperature for 20 h. Then the mixture was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **9** (740 mg, 60%) as a vitreous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.31−7.23 (m, 3H), 7.02 (d, J = 8.3 Hz, 2H), 6.95−6.85 (m, 1H), 5.80 (d, J = 15.7 Hz, 1H), 4.36−4.21 (m, 2H), 3.67 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C), 144.2 (C), 141.9 (CH), 141.1 (C), 140.6 (CH), 136.3 (C), 131.3 (CH), 130.3 (CH), 129.7 (CH), 129.1 (CH), 128.2 (CH), 124.3 (CH), 102.3 (C), 52.6 (CH_2), 51.8 (CH_3), 21.7 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{18}H_{18}O_4NIS$ $[M]^+$ 471.0001, found 471.0010.

*Synthesis of (E)-Methyl 4-(N-(2-Bromophenyl)-4-methylphenylsulfonamido)but-2-enoate (**11**).* NaH (60%) (169 mg, 4.22 mmol) was added to a solution of *N*-(2-bromophenyl)-4-methylbenzenesulfonamide[85] (685 mg, 2.11 mmol) in dry THF (10 mL) under Ar atmosphere. The resulting solution was stirred at room temperature for 15 min. Then a sample of (*E*)-methyl 4-bromobut-2-enoate (0.37 mL, 3.16 mmol) was added to this solution at 0 °C. The resulting solution was stirred at room temperature for 20 h. Then the mixture was diluted with EtOAc, washed with water and brine, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give **11** (250 mg, 29%) as a vitreous solid (53% of starting material was also recovered). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 8.4

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Hz, 1H), 7.33 (d, J = 7.9 Hz, 3H), 7.29−7.20 (m, 2H), 7.01−6.87 (m, 1H), 5.91 (d, J = 15.7 Hz, 1H), 4.39 (d, J = 28.7 Hz, 2H), 3.74 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0 (C), 144.0 (C), 142.2 (CH), 137.6 (C), 136.6 (C), 134.1 (CH), 132.6 (CH), 130.2 (CH), 129.7 (CH), 128.2 (CH), 127.9 (CH), 125.2 (C), 124.0 (CH), 51.9 (CH_2), 51.7 (CH_3), 21.6 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{18}H_{18}O_4NBrS$ $[M]^+$ 423.0140, found 423.0145.

*Synthesis of (E)-Methyl 4-(N-(2-Iodobenzyl)-4-methylphenylsulfonamido)but-2-enoate (**12**).* (*E*)-Methyl 4-bromobut-2-enoate (278 mg, 1.55 mmol) was added to a mixture of *N*-(2-iodobenzyl)-4-methylbenzenesulfonamide[86] (400 mg, 1.03 mmol) and NaH (60%) (62 mg, 1.54 mmol) in THF (12 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 15:85) to give **12** (165 mg, 33%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.3 Hz, 3H), 6.95 (t, J = 7.6 Hz, 1H), 6.61−6.51 (m, 1H), 5.71 (d, J = 15.7 Hz, 1H), 4.39 (s, 2H), 3.90 (d, J = 4.8 Hz, 2H), 3.65 (s, 3H), 2.44 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C), 144.0 (C), 142.0 (CH), 139.6 (CH), 137.8 (C), 136.5 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.8 (CH), 127.3 (CH), 123.7 (CH), 98.8 (C), 56.3 (CH_2), 51.7 (CH_3), 48.8 (CH_2), 21.6 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{19}H_{20}O_4NIS$ $[M]^+$ 485.0158, found 485.0155.

*Synthesis of (E)-Dimethyl 2-(2-Iodobenzyl)-2-(4-oxopent-2-en-1-yl)malonate (**14**).* Methyl vinyl ketone (0.70 mL, 8.49 mmol) was added to a deoxygenated solution of Grubb's second-generation catalyst (25 mg, 0.029 mmol) and dimethyl 2-allylmalonate (0.47 mL, 2.90 mmol) in dry CH_2Cl_2 (8 mL), and the resulting mixture was refluxed for 48 h. The solvent was removed, and the residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give (*E*)-dimethyl 2-(4-oxopent-2-en-1-yl)malonate (275 mg, 45%) as a yellowish oil. Its spectroscopic data were identical to the reported compound.[87]

1-(Bromomethyl)-2-iodobenzene (578 mg, 1.95 mmol) was added to a mixture of (*E*)-dimethyl 2-(4-oxopent-2-en-1-yl)malonate (275 mg, 1.30 mmol) and NaH (60%) (52 mg, 1.30 mmol) in THF (15 mL). The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 3:7) to give **14** (44 mg, 44%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.9 Hz, 1H), 7.28−7.22 (m, 1H), 7.15 (d, J = 7.15 Hz, 1H), 6.91 (t, J = 7.9 Hz, 1H), 6.77−6.66 (m, 1H), 6.01 (d, J = 15.9 Hz, 1H), 3.74 (s, 6H), 3.57 (s, 2H), 2.79 (d, J = 8.6 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2 (C), 170.6 (C), 142.4 (CH), 140.1 (C), 139.0 (C), 134.1 (CH), 130.0 (CH), 129.0 (CH), 128.4 (CH), 103.1 (C), 59.1 (C), 52.8 (CH_3), 43.1 (CH_2), 36.5 (CH_2), 26.8 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{19}O_5I$ $[M]^+$ 430.0277, found 430.0275.

*Synthesis of (E)-N-(2-Iodophenyl)-N-tosylbut-2-enamide (**16**).* (*E*)-But-2-enoyl chloride (0.24 mL, 2.52 mmol) was slowly added to a mixture of Et_3N (0.35 mL, 2.52 mmol) and *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (785 mg, 2.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with CH_2Cl_2, washed with aqueous NH_4Cl, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 20:80) to give **16** (520 mg, 56%) as a vitreous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.99 (dd, J = 7.7, 1.4 Hz, 1H), 7.47 (dt, J = 7.7, 1.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.37 - 7.30 (m, 1H), 7.18 (dt, J = 7.7, 1.4 Hz, 1H), 7.03 (dq, J = 15.0, 7.0 Hz, 1H), 5.41 (d, J = 15.0 Hz, 1H), 2.44 (s, 3H), 1.71 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C), 147.1 (CH), 145.2 (C), 140.7 (CH), 139.2 (C), 136.4 (C), 131.6 (CH), 131.3 (CH), 130.1 (CH), 129.6 (CH), 129.3 (CH), 122.2 (CH), 102.5 (C), 21.8 (CH_3), 18.4 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{17}O_3NIS$ $[M + H]^+$ 441.9974, found 441.9976.

*Synthesis of (E)-N-(2-Bromophenyl)-N-tosylbut-2-enamide (**18**).* (*E*)-But-2-enoyl chloride (0.18 mL, 1.84 mmol) was slowly added to a mixture of Et_3N (0.26 mL, 1.84 mmol) and *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (499 mg, 1.53 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 16 h. Then the mixture was diluted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 2:8) to give **18** (410 mg, 68%) as a white solid. Mp: 160−162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 7.9 Hz, 1H), 7.51−7.36 (m, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.03 (dq, J = 15.0, 6.9 Hz, 1H), 5.43 (d, J = 15.0 Hz, 1H), 2.44 (s, 3H), 1.71 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (C), 147.0 (CH), 145.1 (C), 136.4 (C), 135.6 (C), 134.1 (CH), 132.6 (CH), 131.4 (CH), 129.9 (CH), 129.3 (CH), 128.8 (CH), 125.8 (C), 21.8 (CH_3), 18.4 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{17}H_{17}O_3NBrS$ $[M + H]^+$ 394.0113, found 394.0111.

Representative Procedure for Intramolecular Protocol. Rigorously deoxygenated dry THF (10 mL) was added to a deoxygenated mixture of Cp_2TiCl_2 (0.7 mmol), Mn (8.0 mmol), $NiCl_2$ (0.2 mmol), and PPh_3 (0.4 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 10 min). A solution of the previously synthesized polyfunctionalized substrate (Table 4, starting material, 1.0 mmol) in THF (2 mL) and Me_3SiCl (4.0 mmol) were then added. The reaction mixture was stirred at room temperature for 16 h and then diluted with AcOEt, washed with HCl (10%), and dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash column chromatography (SiO_2, EtO Ac/hexane mixture) to give the corresponding cyclic products (Table 4, product, yield).

Characterization Data of Cyclic Compounds 2, 7, 10, 13, 15, and 17. *Dimethyl 4-(2-Methoxy-2-oxoethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2**).* Colorless oil, 63−72% yield. NMR spectra were identical to the reported data.[83]

*Dimethyl 4-(2-tert-Butoxy-2-oxoethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**7**).* Colorless oil, 56−58% yield. NMR spectra were identical to the reported data.[83]

*Methyl 2-(1-Tosylindolin-3-yl)acetate (**10**).* Vitreous solid, 34−73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.12−6.95 (m, 3H), 4.15−4.05 (m, 1H), 3.69 (s, 3H), 3.68−3.62 (m, 1H), 3.60−3.49 (m, 1H), 2.53 (dd, J = 16.5, 5.1 Hz, 1H), 2.37 (s, 3H), 2.23 (dd, J = 16.5, 9.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (C), 144.3 (C), 141.8 (C), 133.9 (C), 133.8 (C), 129.8 (CH), 129.4 (CH), 128.7 (CH), 127.4 (CH), 124.5 (CH), 124.0 (CH), 55.8 (CH_2), 52.0 (CH_3), 39.4 (CH_2), 36.5 (CH), 21.7 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{18}H_{19}O_4NS$ $[M]^+$ 345.1035, found 345.1035.

*Methyl 2-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate (**13**).* Colorless oil, 58% yield. Compound **13** was isolated as a 5:1 mixture with reduced compound methyl 4-(*N*-benzyl-4-methylphenylsulfonamido)butanoate. See the corresponding ^{1}H NMR spectra in the Supporting Information. Spectroscopic data for compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.31−7.26 (m, 1H), 7.18−7.12 (m, 2H), 7.06−6.99 (m, 1H), 4.61 (d, J = 15.0 Hz, 1H), 3.88−3.82 (m, 1H), 3.82 (d, J = 15.0 Hz, 1H), 3.72 (s, 3H), 3.44−3.37 (m, 1H), 2.91 (dd, J = 16.8, 9.6 Hz, 1H), 2.81 (dd, J = 12.0, 3.0 Hz, 1H), 2.59 (dd, J = 16.8, 4.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8 (C), 143.9 (C), 136.2 (C), 133.2 (C), 131.6 (C), 129.9 (CH), 128.7 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 51.9 (CH_3), 47.8 (CH_2), 47.5 (CH_2), 39.6 (CH_2), 35.1 (CH), 21.7 (CH_3). MS (EI, 70 eV): m/z calcd for $C_{19}H_{21}O_4NS$ $[M]^+$ 359.12, found 359.12.

*Dimethyl 4-(2-Oxopropyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**15**).* Yellowish oil, 51% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22−7.01 (m, 4H), 3.73 (s, 3H), 3.67 (s, 3H), 3.51−3.45 (m, 1H), 3.34 (d, J = 16.0 Hz, 1H), 3.20 (d, J = 16.0 Hz, 1H), 2.97 (dd, J = 17.2, 4.7 Hz, 1H), 2.68 (dd, J = 17.2, 8.3 Hz, 1H), 2.67−2.62 (m, 1H), 2.20 (s, 3H), 1.86 (dd, J = 13.6, 10.2 Hz, 1H). ^{13}C NMR

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(125 MHz, $CDCl_3$): δ 207.3 (C), 172.3 (C), 171.3 (C), 137.8 (C), 134.0 (C), 129.2 (CH), 126.8 (CH), 126.5 (CH), 126.4 (CH), 53.8 (C), 53.0 (CH_3), 52.9 (CH_3), 50.6 (CH_2), 35.4 (CH_2), 34.9 (CH_2), 31.4 (CH), 30.6 (CH_3). HRMS (magnet-EI, 70 eV): *m*/*z* calcd for $C_{17}H_{20}O_5$ $[M]^+$ 304.1311, found 304.1317.

*Ethyl 1-Tosylindolin-2-one (**17**).* Vitreous solid, 48−55% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.38−7.32 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23−7.13 (m, 2H), 3.45 (t, *J* = 5.6 Hz, 1H), 2.41 (s, 3H), 2.06−1.83 (m, 2H), 0.65 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2 (C), 145.7 (C), 140.8 (C), 139.9 (C), 135.5 (C), 129.8 (CH), 128.7 (CH), 128.0 (CH), 124.8 (CH), 124.2 (CH), 113.8 (CH), 46.9 (CH), 24.4 (CH_2), 21.8 (CH_3), 9.5 (CH_3). HRMS (magnet-EI, 70 eV): *m*/*z* calcd for $C_{17}H_{17}O_3NS$ $[M]^+$ 315.0929, found 315.0930.

Synthesis Procedures and Characterization Data of Aryl Halides for Intermolecular Coupling. The following compounds were purchased from commercial sources and used without further purification: iodobenzene, 1-bromo-4-iodobenzene, 1-chloro-4-iodobenzene, methyl 4-iodobenzoate, 4-iodophenol, 3-iodobenzyl alcohol, bromobenzene, and 4-bromophenol.

The following known compounds were synthesized by described methods, and they showed NMR spectra identical to the reported data: 1-iodo-4-methoxybenzene,[88] 4-iodophenyl acetate,[89] *tert*-butyl-((3-iodobenzyl)oxy)dimethylsilane,[90] N-(4-iodophenyl)acetamide,[91] *N*-(2-iodophenyl)acetamide,[92] 1-bromo-4-methoxybenzene,[92] 4-bromophenyl 4-methylbenzenesulfonate,[93] 4-bromophenyl acetate,[94] *N*-(4-bromophenyl)acetamide,[95] and (4-bromophenoxy)-*tert*-butyldimethylsilane.[96]

Synthesis of 4-Iodophenyl 4-Methylbenzenesulfonate. *p*-Toluenesulfonyl chloride (357 mg, 1.87 mmol) was added to a mixture of Et_3N (0.40 mL, 2.81 mmol) and 4-iodophenol (206 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 5 h. Then the mixture was diluted with CH_2Cl_2, washed with water and brine, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 1:9) to give 4-iodophenyl 4-methylbenzenesulfonate (230 mg, 66%) as a white solid. Mp: 101−104 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 6.73 (d, *J* = 7.7 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6 (C), 145.7 (C), 138.8 (CH), 132.2 (C), 130.0 (CH), 128.6 (CH), 124.6 (CH), 91.8 (C), 21.8 (CH_3). HRMS (magnet-EI, 70 eV): *m*/*z* calcd for $C_{13}H_{11}O_3SI$ $[M]^+$ 373.9474, found 373.9471.

Synthesis of *N*-(3-Iodophenyl)acetamide. Acetic anhydride (0.91 mL, 9.59 mmol) was slowly added to a mixture of Et_3N (1.34 mL, 9.59 mmol) and 3-iodoaniline (700 mg, 3.20 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at room temperature for 2 h. Then the mixture was diluted with CH_2Cl_2, washed with water and NaOH (10%), and dried over anhydrous Na_2SO_4. After removal of the solvent, *N*-(3-iodophenyl)acetamide was obtained as a yellowish oil without any further purification (375 mg, 45%).[97] ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (bs, 1H), 7.95 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (C), 139.2 (C), 133.2 (CH), 130.4 (CH), 129.0 (CH), 119.5 (CH), 94.1 (C), 24.5 (CH_3). HRMS (TOF MS ES+): *m*/*z* calcd for C_8H_9NOI $[M + H]^+$ 261.9729, found 261.9733

Synthesis of (((7-Iodohept-6-en-1-yl)oxy)methyl)benzene. PCC (1.11 g, 5.16 mmol) was added to a solution of 6-(benzyloxy)hexan-1-ol[98] (537 mg, 2.58 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 2 h. Then the mixture was submitted to flash chromatography (SiO_2, EtOAc/hexane, 3:7) to give 6-(benzyloxy)hexanal (1.16 g, 33%) as a yellowish oil. Its spectroscopic data were identical to those for the reported compound.[99]

Dry THF (30 mL) was added to a deoxygenated mixture of NaH (60%) (100.8 mg, 2.52 mmol) and (iodomethyl)-triphenylphosphonium iodide (1.34 g, 2.52 mmol), and the reaction mixture was stirred at room temperature for 10 min. Then a solution of compound 6-(benzyloxy)hexanal (260 mg, 1.26 mmol) in THF (2 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with cold water. Then the mixture was diluted with EtOAc, washed with water, and dried over anhydrous Na_2SO_4. The residue was submitted to flash chromatography (SiO_2, EtOAc/hexane, 5:95) to give (((7-iodohept-6-en-1-yl)oxy)methyl)benzene (50 mg, 12%) as a colorless oil. It was isolated as 4:1 mixture of *Z*:*E* isomers. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40−7.24 (m, 5H), 6.57−6.45 (m, 1H, *E*-isomer), 6.23−6.11 (m, 2H, *Z*-isomer), 5.98 (d, *J* = 14.3 Hz, 1H, *E*-isomer), 4.51 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.25−2.10 (m, 2H), 1.74−1.54 (m, 2H), 1.54−1.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (CH), 138.8 (C), 128.5 (CH), 127.7 (CH), 82.5 (CH), 73.0 (CH_2), 70.4 (CH_2), 34.8 (CH_2), 29.7 (CH_2), 27.9 (CH_2), 25.9 (CH_2). HRMS could not be obtained.

General Procedure for Intermolecular Coupling of Aryl Iodide Derivatives. Rigorously deoxygenated dry THF (10 mL) was added to a previously deoxygenated mixture of Cp_2TiCl_2 (0.7 mmol), Mn (8.0 mmol), $NiCl_2$ (0.2 mmol) ,and PPh_3 (0.4 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 10 min). A solution of the corresponding aryl iodide (1.0 mmol) in THF (2 mL), methyl acrylate (10 mmol), and Me_3SiCl (4.0 mmol) were then added. The reaction mixture was stirred at room temperature for 16 h and then diluted with EtOAc, washed with HCl (10%), and dried over anhydrous Na_2SO_4, and the solvent removed. The residue was submitted to flash column chromatography (SiO_2, EtOAc/hexane mixtures) to give the corresponding final products.

General Procedure for Intermolecular Coupling of Aryl Bromide Derivatives. Rigorously deoxygenated dry THF (10 mL) was added to a previously deoxygenated mixture of Cp_2TiCl_2 (0.7 mmol), Mn (8.0 mmol), $NiCl_2$ (0.2 mmol), and PPh_3 (0.4 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 10 min). A solution of the corresponding aryl bromide (1.0 mmol) in THF (2 mL), methyl acrylate (or *tert*-butyl acrylate) (10 mmol), and Me_3SiCl (4.0 mmol) were then added. The reaction mixture was stirred at 50 °C for 16 h and then diluted with EtOAc, washed with HCl (10%), and dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was submitted to flash column chromatography (SiO_2, EtOAc/hexane mixtures) to give the corresponding final products.

Characterization Data of Intermolecular Coupling Products 19−38. *Methyl 3-Phenylpropanoate (**19**).* Colorless oil; 61% yield. NMR spectra were identical to the reported data.[100]

*3-Phenylpropanenitrile (**20**).* Colorless oil; 21% yield. NMR spectra were identical to the reported data.[100]

*4-Phenyltetrahydro-2H-pyran-2-one (**21**).* Yellowish oil; 41% yield. NMR spectra were identical to the reported data.[101]

*tert-Butyl 3-Phenylpropanoate (**22**).* Colorless oil; 42% yield. NMR spectra were identical to the reported data.[102]

*Methyl 3-(4-(Tosyloxy)phenyl)propanoate (**23**).* Vitreous solid; 65% yield (from aryl iodide), 67% yield (from aryl bromide). Compound **23** was isolated as a 10:1 mixture with methyl 3-(4-tosylphenyl)acrylate. See the corresponding ^1H NMR in the Supporting Information. Spectroscopic data of **23**. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.56 (s, 3H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0 (C), 148.2 (C), 145.4 (C), 139.6 (C), 132.6 (C), 129.8 (CH), 129.5 (CH), 128.6 (CH), 122.4 (CH), 51.7 (CH_3), 35.5 (CH_2), 30.3 (CH_2), 21.8 (CH_3). HRMS (magnet-EI, 70 eV): *m*/*z* calcd for $C_{17}H_{18}O_5S$ $[M]^+$ 334.0875, found 334.0877.

*Methyl 3-(4-Methoxyphenyl)propanoate (**24**).* Vitreous solid; 38% yield (from aryl iodide), 70% yield (from aryl bromide). NMR spectra were identical to the reported data.[103]

*Methyl 3-(4-Bromophenyl)propanoate (**25**).* Yellowish oil; 40% yield. NMR spectra were identical to the reported data.[104]

*Methyl 3-(4-Acetoxyphenyl)propanoate (**26**).* Yellowish oil; 46% yield (from aryl iodide), 37% yield (from aryl bromide). ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 3.67 (s, 3H), 2.95 (t, *J* = 7.7 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H),

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2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3 (C), 169.6 (C), 149.2 (C), 138.2 (C), 129.4 (CH), 121.6 (CH), 51.7 (CH_3), 35.7 (CH_2), 30.4 (CH_2), 21.2 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{12}H_{14}O_4$ $[M]^+$ 222.0892, found 222.0882.

Methyl 3-(4-Chlorophenyl)propanoate (27). Yellowish oil; 56% yield. NMR spectra were identical to the reported data.[105] Compound **27** was isolated as a 10:1 mixture with methyl 3-(4-chlorophenyl)-acrylate. See the ^{1}H NMR in the Supporting Information.

Methyl 4-(3-Methoxy-3-oxopropyl)benzoate (28). Colorless oil; 63% yield. NMR spectra were identical to the reported data.[106] Compound **28** was isolated as a 15:1 mixture with methyl 3-(4-carboxymethylphenyl)acrylate. See the ^{1}H NMR in the Supporting Information.

Methyl 3-(3-(((tert-Butyldimethylsilyl)oxy)methyl)phenyl)-propanoate (29). Yellowish oil; 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−6.90 (m, 4H), 4.66 (s, 2H), 3.61 (s, 3H), 2.90 (t, J = 7.8 Hz, 2H), 2.57 (t, J = 7.8 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8 (C), 140.5 (C), 128.5 (CH), 126.9 (CH), 126.1 (CH), 124.2 (CH), 65.0 (CH_2), 51.6 (CH_3), 35.8 (CH_2), 31.1 (CH_2), 26.1 (CH_3), 18.5 (C), −5.1 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{13}H_{19}O_3Si$ $[M-C_4H_9]^+$ 251.1103, found 251.1098.

Methyl 3-(4-Hydroxyphenyl)propanoate (30). Colorless oil; 59% yield. NMR spectra were identical to the reported data.[107]

Methyl 3-(3-(Hydroxymethyl)phenyl)propanoate (31). Colorless oil; 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (m, 4H), 4.60 (s, 2H), 3.62 (s, 3H), 2.91 (t, J = 7.8 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (C), 141.3 (C), 140.8 (C), 128.7 (CH), 127.5 (CH), 126.9 (CH), 125.0 (CH), 65.2 (CH_2), 51.7 (CH_3), 35.6 (CH_2), 30.9 (CH_2). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{11}H_{14}O_3$ $[M]^+$ 194.0943, found 194.0943.

Methyl 3-(4-Acetamidophenyl)propanoate (32). 71% yield (from aryl iodide), 48% yield (from aryl bromide). Yellowish solid. Mp: 131−133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (bs, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.64 (s, 3H), 2.88 (t, J = 7.7 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (C), 168.9 (C), 136.4 (C), 136.3 (C), 128.7 (CH), 120.4 (CH), 51.7 (CH_3), 35.8 (CH_2), 30.4 (CH_2), 24.4 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{12}H_{15}O_3N$ $[M]^+$ 221.1052, found 221.1050.

Methyl 3-(3-Acetamidophenyl)propanoate (33). Vitreous solid; 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.4 Hz, 1H), 3.63 (s, 3H), 2.86 (t, J = 7.7 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (C), 169.1 (C), 141.3 (C), 138.4 (C), 129.0 (CH), 124.1 (CH), 119.9 (CH), 118.1 (CH), 51.7 (CH_3), 35.5 (CH_2), 30.9 (CH_2), 24.4 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{12}H_{15}O_3N$ $[M]^+$ 221.1052, found 221.1048.

Methyl 3-(2-Acetamidophenyl)propanoate (34). 22% yield. White solid. Mp: 134−137 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (bs, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 3.65 (s, 3H), 2.88 (t, J = 7.7 Hz, 2H), 2.71 (t, J = 7.7 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4 (C), 169.0 (C), 135.7 (C), 132.6 (C), 129.9 (CH), 127.3 (CH), 125.5 (CH), 124.9 (CH), 52.2 (CH_3), 35.3 (CH_2), 25.3 (CH_2), 24.3 (CH_3). HRMS (magnet-EI, 70 eV): m/z calcd for $C_{12}H_{15}O_3N$ $[M]^+$ 221.1052, found 221.1053.

tert-Butyl 3-(4-((tert-Butyldimethylsilyl)oxy)phenyl)propanoate (35). Yellowish oil; 69% yield. NMR spectra were identical to the reported data.[108]

tert-Butyl 3-(4-Hydroxyphenyl)propanoate (36). Yellowish oil; 47% yield. NMR spectra were identical to the reported data.[109]

tert-Butyl 4-Phenylpent-4-enoate (37). Yellowish oil; 35% yield. NMR spectra were identical to the reported data.[110]

(Z)-tert-Butyl 8-(Benzyloxy)oct-4-enoate (38). Yellowish oil; 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.22 (m, 4H), 5.48−5.28 (m, 2H), 4.50 (s, 1H), 3.46 (t, J = 6.6 Hz, 1H), 2.38−2.19 (m, 2H), 2.12−1.97 (m, 2H), 1.71−1.57 (m, 2H), 1.53−1.22 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7 (C), 138.8 (C), 131.1 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 80.3 (C), 73.0 (CH_2), 70.5 (CH_2), 35.7 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 28.3 (CH_3), 27.3 (CH_2), 26.0 (CH_2), 23.1 (CH_2).

Transmission Electron Microscopy study. Obtaining particles. Rigorously deoxygenated dry THF (10 mL) was added to a previously deoxygenated mixture of Cp_2TiCl_2 (24 mg, 0.1 mmol) and Mn (63 mg, 1.1 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 10 min). The mixture was allowed to stand unperturbed, and then 8 mL of green supernatant was separated into a deoxygenated Schlenk flask. After that, 5 mL of a deoxygenated THF solution of $Ni(acac)_2$ (4 mM) was added. An instant color change to dark green was observed, and within the next 15 min a dark gray precipitate was produced. The mixture was let to stand unperturbed overnight, and a black precipitated was obtained. **Sample Preparation for TEM Analysis**. The black precipitate obtained was dispersed in MeOH. A drop of the suspension was transferred to a gold grid and MeOH removed by evaporation. The grid was checked for specimen quality under an optical microscope before analysis in the electron microscope. **TEM Analysis.** TEM images were obtained with a high-resolution transmission electron microscope and STEM instrument operated at 200 kV and equipped with a EDX model EDAX. Representative micrographs of the solid particles are shown in Figure 1. The electron micrographs were enlarged, and the diameter of the metal particles was measured. The particle size determination was done by randomly measuring the size of several particles on the TEM micrographs. Particles in the range of 80−150 nm were found to be mainly nickel on EDX analysis. The presence of Ti, Mn, and Cl was also observed. The particles were supported in a gold grid, and although a copper grid is often used in this instrument, small amounts of Cu and Au are also observed.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis overview and copies of UV−vis absorption, ^{1}H NMR, ^{13}C NMR, and EDX spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(58) See the Experimental Section for further details.
(59) The results of entries 11 and 12 (Table 4) are unusual because normal conjugate addition would lead to 6-membered rings. However a 5-*exo*-*trig* radical-type cyclization would lead to 5-membered rings. In this case, involvement of radical-type Ni(I) species cannot be ruled out.
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(64) Typical reaction conditions for the intermolecular coupling of aryl bromides with acrylates are as follows: aryl bromide (1.0 equiv), Cp_2TiCl_2 (0.7 equiv), $NiCl_2$ (0.2 equiv), PPh_3 (0.4 equiv), Mn (8 equiv), Me_3SiCl (4 equiv), THF, 50 °C, 16 h. See the Supporting Information for further experimental details.
(65) In the case of vinyl halides, coupling product yields were lower, mainly due to loss as reduction products.
(66) Treatment of compound **1** (1.0 mmol) with $Ni(cod)_2$ (2.0 mmol), PPh_3 (4.0 mmol), Me_3SiCl (4.0 mmol), THF, rt, 16 h led to compound **2** in 70% yield, and an additional 9% of starting material was recovered.
(67) UV−vis spectra are included in the Supporting Information. It was not possible to use $NiCl_2$ due to solubility issues. $Ni(acac)_2$ is very soluble in THF.
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