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Merging C–C σ-bond activation of cyclobutanones with CO_2 fixation *via* Ni-catalysis†

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A carboxylative Ni-catalyzed tandem C–C σ-bond activation of cyclobutanones followed by CO_2-electrophilic trapping is documented as a direct route to synthetically valuable 3-indanone-1-acetic acids. The protocol shows an adequate functional group tolerance and useful chemical outcomes (yield up to 76%) when $AlCl_3$ is adopted as an additive. Manipulations of the targeted cyclic scaffolds and a mechanistic proposal based on experimental evidence complete the investigation.

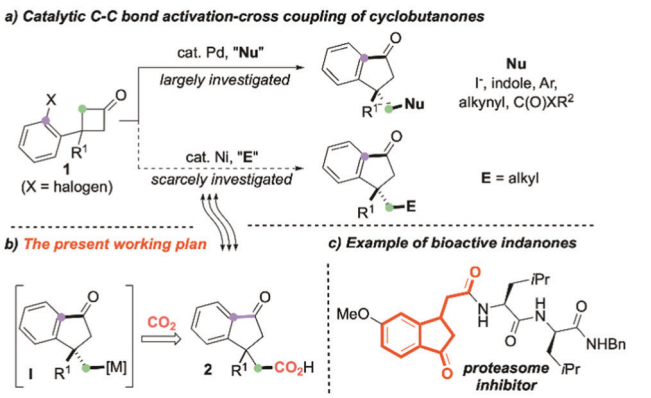
Nowadays, the employment of strained rings in site selective C–C σ-bond activation procedures is receiving growing credit for generating chemical diversity, *via* catalytic tandem functionalization processes.[1]

In this context, transition-metal catalyzed σ-bond activation of cyclobutanones represents an important landmark in the field, resulting in a direct synthetic route towards densely functionalized scaffolds.[2] In this segment, following the pioneering reports by Dong,[3] Cramer[4] and Murakami,[5] several Pd-catalyzed sequential ring-opening/nucleophilic cross-couplings have been documented (Scheme 1a).[6] On the contrary, the employment of more convenient, largely available and bench-stable electrophilic trapping agents is still basically unexplored in the field. In fact, to the best of our knowledge, the recent Ni-catalyzed cyclobutanone C–C activation, studied by Wang, represents the only ring-opening/cross electrophile coupling (*i.e.* alkyl bromides and iodo-arenes as starting materials) reported so far.[7]

With the aim to address this important lack in the literature, we directed our attention to carbon dioxide as an emerging electrophilic C1-synthon in organic chemistry. Large abundance, non-toxicity and low cost justify the exponential efforts towards the realization of direct catalytic tools for CO_2 fixation into organic scaffolds.[8] In particular, the valorization of carbon dioxide *via* metal-, metal-free, photo- and electrocatalyzed cascade carboxylative processes has rapidly emerged as a valuable route towards molecular complexity.[9–11]

In this context, and in conjunction with our recent research interests towards the catalytic conversion of CO_2 into added value carbonylic as well as carboxylic compounds,[12] we envisioned the unprecedented employment of carbon dioxide as a late-stage electrophilic quencher of the incipient organometallic intermediate **I**, that might be directly accessible *via* metal-assisted C–C σ-bond activation of cyclobutanones (Scheme 1b). Remarkably, this process would result in a new reductive cross-electrophile coupling to rapidly access synthetically flexible 3-indanone-1-acetic acid scaffolds **2**[13] by avoiding the use of hazardous carbon monoxide or its surrogates.[14]

In this report we disclose our initial findings in the field by electing 3-(2-haloaryl)cyclobutanones **1** as model substrates and nickel as a first-row transition-metal catalyst.



Scheme 1 (a) C–C bond activation-cross coupling of 3-(2-aryl)cyclobutanones: nucleophilic and electrophilic approaches. (b) The present working plan. (c) An example of a bioactive 3-indanone-1-acetic acid derivative.

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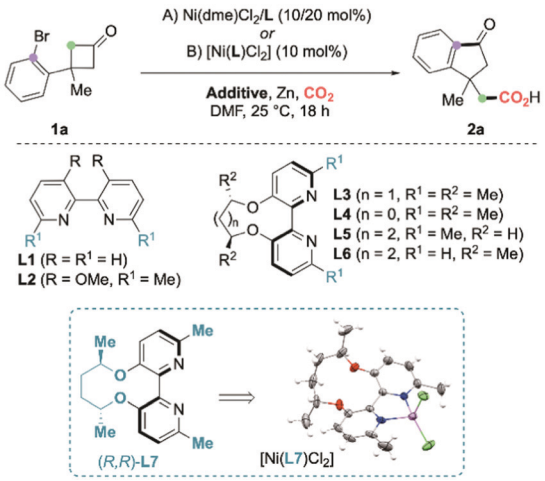
Table 1 Optimization of the reaction conditions



Entry	L	Conditions[a]	Additive	Yield[b] (%)
1	**L1**	A	None	NR
2	**L1**	A	LiCl	NR
3	**L1**	A	$MgCl_2$	15
4	**L1**	A	$AlCl_3$	30
5	**L1**	A	HCl[c]	NR
6	**L1**	A	$Al(OTf)_3$	NR
7	**L1**	A	$Al(OTf)_3$ + LiCl[d]	NR
8	**L2**	A	$AlCl_3$	43
9	**L3**	B	$AlCl_3$	59
10	**L4**	B	$AlCl_3$	Traces
11	**L5**	B	$AlCl_3$	12
12	**L6**	B	$AlCl_3$	18
13	**L7**	B	$AlCl_3$	64
14[e]	**L7**	B	$AlCl_3$	70
15[f]	**L7**	B	$AlCl_3$	45

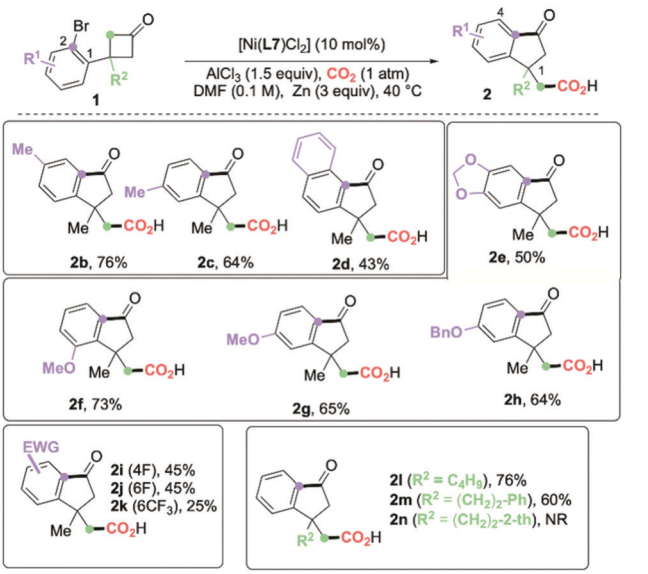
[a] Reaction conditions A and B: **1a** (0.1 mmol, 0.1 M), additive (0.15 mmol), Zn (0.3 mmol), CO_2 (1 atm). [b] Isolated yield after flash chromatography. [c] 4 mol% of HCl was used (4 M in 1,4-dioxane). [d] LiCl = 0.45 mmol. [e] 40 °C. [f] 60 °C. NR = no reaction.

Aiming at optimizing the reaction conditions, we initially reacted the model substrate **1a** with $[Ni(dme)Cl_2]$ (10 mol%) and 2,2′-bipyridine (20 mol%) as the ligand, in DMF under a CO_2 atmosphere at room temperature. Under these conditions, no product was formed and a small amount of dehalogenated starting material (**7a**, *vide infra*) was observed, along with substantial recovery of untouched **1a** (entry 1, Table 1). We reasoned that the addition of a Lewis/Brønsted acid could favor the overall process *via* activation of the carbonyl unit (entries 2–5). Interestingly, although no conversion was recorded with mono-valent lithium chloride (entry 2, complete recovery of **1a**), when magnesium chloride was employed (1.5 equiv.) the desired product **2a** was observed, albeit in low yield (15%, entry 3). A significant improvement in the isolated yield of **2a** (30%) was observed by adopting a stronger Lewis acid, namely $AlCl_3$ (entry 4), which proved to be the best additive (see SI for further screening). We then excluded that any adventitious traces of HCl deriving from $AlCl_3$ could trigger a Brønsted-acid catalysis (entry 5).

It is worth noting that the presence of $AlCl_3$ is mandatory for the desired process to proceed, as related $Al(OTf)_3$ was found to be ineffective, even in the presence of an external chloride source (entries 6, 7, complete recovery of **1a**). Then, we turned our attention to the role of the ligand **L**. Encumbered and electron-rich ligand **L2** (entry 8) provided **2a** in higher yield than **L1** (43% yield). Prompted by these achievements, we focused our attention on *C*2-symmetric ligands **L3-7**[15] sharing similar tethering backbones (entries 9–13). Our investigation pointed to bipyridine (*R*,*R*)-**L7** as the optimal one, delivering **2a** in 64% yield (entry 13).[16] This ligand displays a 6,6′-Me_2 substitution pattern and a cyclic tethering 3,3′-ether backbone, readily accessible from (*S*,*S*)-2,5-hexanediol (see ESI† for details). Aiming at obtaining high reproducibility in the chemical outcomes we isolated the precatalyst $[Ni(\mathbf{L7})Cl_2]$ in 90% yield by reacting enantiopure (*R*,*R*)-**L7** and $Ni(dme)Cl_2$ in DMF. The resulting brown solid was fully characterized. Single-crystal X-ray diffraction showed a 1 : 1 Ni : **L7** ratio with the Ni atom displaying a distorted tetrahedral geometry being coordinated by two chloride ligands and two pyridinic nitrogen atoms with a (N–Ni–N) bite angle of 83.0(1)°. The dihedral angle between the two pyridine rings is significant (27.6(2)°) as a consequence of the formation of the ten-membered ring in **L7**. While ligand **L3**, formally deriving from (*S*,*S*)-2,4-pentanediol, performed similarly to **L7** (59% yield, entry 9), (*S*,*S*)-2,3-butanediol-derived **L4** failed to promote the desired reaction (entry 10), highlighting the importance of the size of the cyclic ether scaffold (Scheme 2).

Similarly, ligands **L5**, lacking methyl groups on the tethering moiety (entry 11) and **L6**, lacking 6,6′-methyl groups (entry 12) delivered the desired product in low yields.

Finally, a slight improvement in the catalytic performance was observed by running the reaction at 40 °C (70% yield, entry 14) while a higher temperature proved detrimental (45% yield at 60 °C, entry 15).



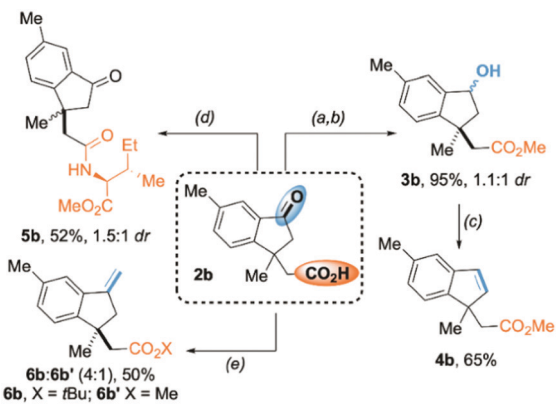
Scheme 2 Generality of the Ni-catalyzed tandem C–C bond activation-CO_2 fixation process.

With the optimal reaction conditions in hand (Table 1, entry 14, conditions B), we assessed the generality of the process by subjecting a range of 3-(2-bromoaryl)cyclobutanones **1b–n** to the carboxylative ring-opening process. Hydrocarbyl (**1b–d**) as well as electron-donating (**1e–h**) substituents could be effectively accommodated at positions 4-, 5- and 6- of the aromatic ring, providing the corresponding 3-indanone-1-acetic acids **2b–h** up to high yields (43–76%).

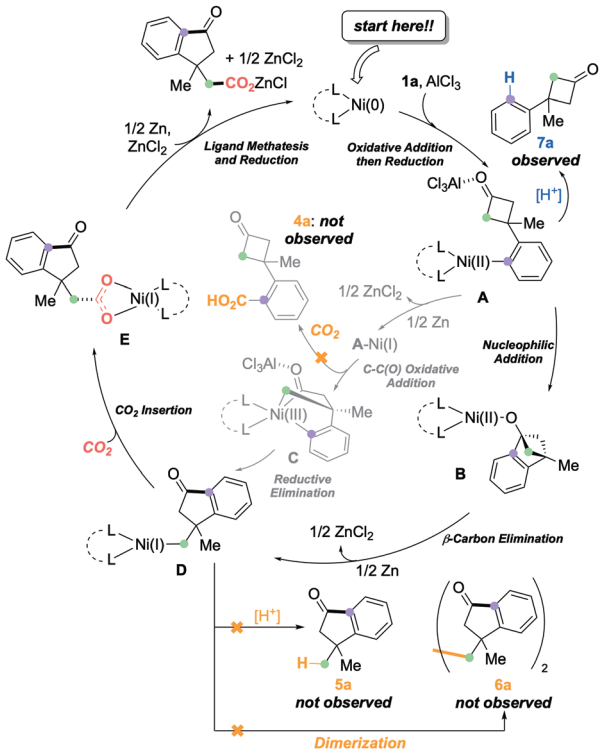
On the other hand, electron-withdrawing groups (*i.e.* F and CF_3) on the 2-bromoaryl moiety of cyclobutanones **1i–k**, led to a slight decrease in efficiency (25–45% yield), probably due to a reduced nucleophilicity of the corresponding Ar–Ni(II) intermediates (*vide infra*). Additionally, the possibility to decorate the quaternary stereogenic center at the C1-position (**2**) with different alkyl groups was also successfully demonstrated. In this regard, 3-indanone-1-acetic acids **2l** and **2m**, carrying a *n*-butyl and a phenethyl substituent respectively, were formed in high yield. On the contrary, thienyl-substituted substrate **1n** was unproductive in the reactive sequence, probably due to a poisoning coordination operated by the sulfur-based heterocycle on the catalytically active metal species.

To prove the synthetic utility and chemical versatility of the newly synthesized 3-indanone-1-acetic acids **2**, product **2b** was subjected to a range of relevant transformations (Scheme 3). After esterification of the carboxylic moiety (a), reduction of the keto-group with $NaBH_4$ afforded alcohol **3b** in quantitative yield as an equimolar mixture of diastereoisomers (b).

A successive dehydration (*p*-TSA, c) was also documented, yielding the corresponding indene **4b** in 65% yield. On the other hand, Wittig olefination rendered methylene–indanes **6b–6b′** carrying an exocyclic C–C double bond, chemoselectively. Importantly, as a proof-of-concept for bioconjugation of **2**, we showed that the carboxylic acid moiety of **2b** underwent peptide-bond formation with isoleucine methyl ester (H-Ile-OMe) to afford amide **5b** in 52% yield and 1.5 : 1 *dr*.



Scheme 3 Transformations of compound **2b**. Conditions: (a) H_2SO_4 (1 drop), MeOH, reflux, 18 h. (b) $NaBH_4$ (3 equiv.), MeOH, r.t., 1 h. (c) *p*-TSA (1 equiv.), PhMe, reflux, 18 h. (d) H-Ile-OMe (1 equiv.), EDC·HCl (1 equiv.), TEA (3 equiv.), HOBt (1.2 equiv.), DCM/DMF 3 : 1, 25 °C, 18 h. (e) Ph_3PCH_3I (2 equiv.), KO*t*Bu (2.5 equiv.), THF, 0 °C to reflux, 18 h. *p*-TSA = *p*-toluene sulfonic acid; EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; TEA = triethylamine; HOBt = hydroxybenzotriazole.



Scheme 4 Mechanistic proposal.

Mechanistically, the catalytic cycle depicted in Scheme 4 is proposed based on experimental evidence as well as previous reports on metal-catalyzed C–C bond activation-cross coupling reactions of cyclobutanones.[6,7] An aryl–Ni(II) species **A** could be conveniently formed *via* initial oxidative insertion of a Ni(0)-complex on **1a**.[17] This organometallic intermediate can undergo C=O nucleophilic addition on the LA-activated carbonyl unit to give the alkoxy-Ni intermediate **B**.[18] Alternatively, Zn-mediated reduction towards **A**-Ni(I) can occur, with subsequent delivery of the adduct **C** *via* C–C(O) oxidative insertion. Given the fundamental role played by $AlCl_3$ in the present reaction, and the absence of benzoic acid **8a**, we could tentatively propose intermediate **B** as the more likely formed.[19,20]

Subsequently, β-carbon elimination, followed by Zn-mediated reduction, would result to the alkyl-Ni(I) species **D**. Trapping of CO_2[21] and regeneration of the catalytically active Ni(0)-catalyst would close the reaction machinery. Importantly, while the formation of substantial amounts of dehalogenation by-product **7a** were often observed in the crude reaction mixtures, conceivable by-products **9a**/**10a** (often encountered in tandem carboxylation processes) were never formed in detectable amounts in the present methodology. This suggests that the C=O insertion step might be kinetically demanding and the carboxylation of alkylnickel(I) intermediate **D** is faster than protodenickelation (**9a**) and dimerization processes (**10a**).[22] This conclusion is also in line with the superior catalytic performance displayed by electron-rich bypyridines.

In conclusion, we have documented an unprecedented carboxylative nickel-catalyzed C–C σ-bond activation of

cyclobutanones combined with final electrophilic trapping of CO_2 at low pressure. The protocol enabled a range of synthetically useful functionalized 3-indanone-1-acetic acids to be prepared in moderate to high yield (up to 76%). Proof of the synthetic flexibility of the resulting indanones and mechanistic insights completed the present investigation. Studies towards the realization of an enantioselective variant of the present protocol are currently underway in our laboratories and will be presented in due course.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) M. Suginome, T. Matsuda and Y. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 11015–11016; (*b*) T. Matsuda and H. Kirikae, *Organometallics*, 2011, **30**, 3923–3925; (*c*) T. Xu, A. Dermenci and G. Dong, *Top. Curr. Chem.*, 2014, **346**, 233–257; (*d*) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410; (*e*) N. Murakami and N. Ishida, *J. Am. Chem. Soc.*, 2016, (138), 13759–13769; (*f*) M. H. Shaw and J. F. Bower, *Chem. Commun.*, 2016, **52**, 10817–10829; (*g*) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404–9432.

2 (*a*) U.-H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446–447; (*b*) T. Ito, T. Tanaka, M. Iinuma, K. Nakaya, Y. Takahashi, R. Sawa, J. Murata and D. Darnaedi, *J. Nat. Prod.*, 2004, **67**, 932–937; (*c*) R. E. McDevitt, M. S. Malamas, E. S. Manas, R. J. Unwalla, Z. Xu, C. P. Miller and H. A. Harris, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3137–3142; (*d*) A. Morrell, M. Placzek, S. Parmley, B. Grella, S. Antony, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2007, **50**, 4388–4404; (*e*) B. Alcaide, P. Almendros and C. Lázaro-Milla, *Chem. – Eur. J.*, 2019, **25**, 7547–7552; (*f*) Y. Chen, Z. Ding, Y. Wang, W. Liu and W. Kong, *Angew. Chem., Int. Ed.*, 2021, **60**, 5273–5278; (*g*) F.-S. He, P. Bao, F. Yu, L.-H. Zeng, W.-P. Deng and J. Wu, *Org. Lett.*, 2021, **23**, 7472–7476.

3 (*a*) M. K. Ko and G. Dong, *Nat. Chem.*, 2014, **6**, 739–744; (*b*) X. Zhou and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 13715–13721; (*c*) X. Zhou and G. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 15091–15095.

4 (*a*) L. Souillart, E. Parker and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 3001–3005; (*b*) L. Souillart and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9640–9644; (*c*) E. Parker and N. Cramer, *Organometallics*, 2014, **33**, 780–787.

5 (*a*) M. Murakami, H. Amii and Y. Ito, *Nature*, 1994, **370**, 540–541; (*b*) T. Matsuda, M. Shigeno, M. Makino and M. Murakami, *Org. Lett.*, 2006, **8**, 3379–3381; (*c*) T. Matsuda, M. Shigeno and M. Murakami, *J. Am. Chem. Soc.*, 2007, **129**, 12086–12087; (*d*) L. Liu, N. Ishida and M. Murakami, *Angew. Chem., Int. Ed.*, 2012, **51**, 2485–2488.

6 For a representative collection of examples see: (*a*) Y.-L. Sun, X.-B. Wang, F.-N. Sun, Q.-Q. Chen, J. Kao, Z. Xu and L.-W. Xu, *Angew. Chem., Int. Ed.*, 2019, **58**, 6747–6751; (*b*) J. Kao, L. Chen, F.-N. Sun, Y.-L. Sun, K.-Z. Jiang, K.-F. Yang, Z. Xu and L.-W. Xu, *Angew. Chem., Int. Ed.*, 2019, **58**, 897–901; (*c*) F.-N. Sun, W.-C. Yang, X.-B. Chen, Y.-L. Sun, J. Kao, Z. Xu and L.-W. Xu, *Chem. Sci.*, 2019, **10**, 7579–7583; (*d*) W.-C. Yang, X.-B. Chen, K.-L. Song, B. Wu, W.-E. Gan, Z.-J. Zheng, J. Kao and L.-W. Xu, *Org. Lett.*, 2021, **23**, 1309–1314.

7 D. Ding, H. Dong and C. Wang, *iScience*, 2020, **23**, 101017.

8 (*a*) M. Aresta, *Carbon Dioxide as Chemical Feedstock*, Wiley VCH, Weinheim, 2010; (*b*) T. Sakakura, J.-C. Choi and Y. Yasuda, *Chem. Rev.*, 2007, **107**, 2365–2387; (*c*) J. R. Cabrero-Antonino, R. Adam and M. Beller, *Angew. Chem., Int. Ed.*, 2019, **58**, 12820–12838; (*d*) S. Dabral and T. Schaub, *Adv. Synth. Catal.*, 2019, **361**, 223–246.

9 (*a*) Q. Liu, L. Wu, R. Jackstell and M. Beller, *Nat. Commun.*, 2015, **6**, 5933; (*b*) M. Aresta, A. Dibenedetto and A. Angelini, *Chem. Rev.*, 2014, **114**, 1709–1742.

10 (*a*) M. Börjesson, T. Moragas, D. Gallego and R. Martin, *ACS Catal.*, 2016, **6**, 6739–6749; (*b*) J. Luo and I. Larrosa, *ChemSusChem*, 2017, **10**, 3317–3332; (*c*) M. Gaydou, T. Moragas, F. Julià-Hernàndez and R. Martin, *J. Am. Chem. Soc.*, 2017, **139**, 12161–12164; (*d*) Y.-G. Chen, X.-T. Xu, K. Zhang, Y.-Q. Li, L.-P. Zhang, P. Fang and T. S. Mei, *Synthesis*, 2018, 35–48; (*e*) Z. Zhang, J.-H. Ye, T. Ju, L.-L. Liao, H. Huang, Y.-Y. Gui, W.-J. Zhou and D.-G. Yu, *ACS Catal.*, 2020, **10**, 10871–10885; (*f*) X. Gou, Y. Wang, J. Chen, G. Li and J.-B. Xia, *Chin. J. Org. Chem.*, 2020, **40**, 2208–2220; (*g*) J.-H. Ye, T. Ju, H. Huang, L.-L. Liao and D.-G. Yu, *Acc. Chem. Res.*, 2021, **54**, 2518–2531; (*h*) Y. Yi, W. Hang and C. Xi, *Chin. J. Org. Chem.*, 2021, **41**, 80–93.

11 For our recent review see: G. Bertuzzi, A. Cerveri, L. Lombardi and M. Bandini, *Chin. J. Chem.*, 2021, **39**, 3116–3126.

12 (*a*) A. Cerveri, S. Pace, M. Monari, M. Lombardo and M. Bandini, *Chem. – Eur. J.*, 2019, **25**, 15272–15276; (*b*) A. Cerveri, R. Giovanelli, D. Sella, R. Pedrazzani, M. Monari, O. N. Faza, C. S. Lòpez and M. Bandini, *Chem. – Eur. J.*, 2021, **27**, 7657–7662.

13 P. Jimonet, Y. Ribeill, G. A. Bohme, A. Boireau, M. Chevé, D. Damour, A. Doble, A. Genevois-Borella, F. Herman, A. Imperato, S. Le Guern, F. Manfré, J. Prat, J. C. R. Randle, J.-M. Stutzmann and S. Mignani, *J. Med. Chem.*, 2000, **43**, 2371–2381.

14 During the preparation of the manuscript, similar bicyclic scaffolds were obtained under Pd-catalyzed manipulation of iodo-arenes in the presence of CO and CO surrogates: (*a*) C. Chen, H. Zhao, Y. Pu, L. Tang, J. Wang and Y. Shang, *Chem. Commun.*, 2021, **57**, 12944–12947; (*b*) K.-L. Song, B. Wu, W.-E. Gan, W.-C. Yang, X.-B. Chen, J. Kao and L.-W. Xu, *Org. Chem. Front.*, 2021, **8**, 3398–3403.

15 X. Gao, B. Wu, W.-X. Huang, M.-W. Chen and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 11956–11960.

16 The enantiomeric excess of **2a** prepared in the presence of enantiopure ligands **L3**, **L4**, **L6** and **L7** was in all cases lower than 20% (18% ee with ligand **L7**). Rac-2,5-hexanediol is commercialized only as a 1 : 1 mixture with the *meso*-isomer. Preparation of the corresponding 2,2′-bipyridine ligand led to an inseparable mixture of **rac-L7** and ***meso*-L7**, that proved ineffective in the present transformation. Therefore, enantiopure (*R*,*R*)-**L7** was selected as the optimal ligand.

17 At present, a catalytic process involving a Ni(I) species undergoing oxidative addition with **1a** cannot be ruled out.

18 K. J. Garcia, M. M. Gilbert and D. J. Weix, *J. Am. Chem. Soc.*, 2019, **141**, 1823–1827 and references therein. The possible involvement of the *in situ* generated Zn(II) salts in co-activating the cyclobutanone ring towards Ni–Ar condensation cannot be ruled out at present.

19 At present, a conclusive rationale for the specific role of $AlCl_3$ in promoting the carboxylation reaction is not available. Among many possible roles, both facilitation of the final de-nickelation steps from the carboxylate intermediate and the possible electrophilic co-activation of CO_2 cannot be excluded: (*a*) M. Gu and Z. Cheng, *Ind. Eng. Chem. Res.*, 2014, **53**, 9992–9998; (*b*) M. Gu and Z. Cheng, *J. Mater. Sci. Eng.*, 2015, **3**, 103–108.

20 For an example of different impacts of Cl^- and OTf^- in carboxylation reactions see: D. J. Charboneau, G. W. Brudvig, N. Hazari, H. M. C. Lant and A. K. Saydjari, *ACS Catal.*, 2019, **9**, 3228–3241.

21 (*a*) F. S. Menges, S. M. Craig, N. Tötsch, A. Blumfield, S. Ghosh, H.-J. Krüger and M. A. Johnson, *Angew. Chem., Int. Ed.*, 2016, **55**, 1282–1285; (*b*) T. Fujihara, K. Nogi, T. Xu, J. Terao and Y. Tsuji, *J. Am. Chem. Soc.*, 2012, **134**, 9106–9109.

22 R. J. Somerville, C. Odena, M. F. Obst, N. Hazari, K. H. Hopmann and R. Martin, *J. Am. Chem. Soc.*, 2020, **142**, 10936–10941.

